REMARKS

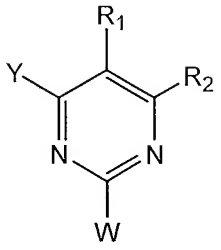
Claims 1-27, 31, 32, 37-43, 45, 46, and 54-58 are pending in the application. The indication of allowance of Claims 1-27, 31, 32, 37-43, 45, and 46 is noted with appreciation. Claims 54-58 have been rejected. Claims 54 and 56 have been amended. Reconsideration and allowance of Claims 1-27, 31, 32, 37-43, 45, 46, and 54-58 in view of the above amendments and following remarks is respectfully requested.

The Rejection of Claims 54-58 Under 35 U.S.C. § 103(a)

Claims 54-58 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over DE 2341925, issued to Narr et al., in view of Caine et al., *Cancer* *98*(8):1578-1586, 2003. Withdrawal of the rejection is requested for the following reasons.

Claims 54 and 56 have been amended. Claim 55 depends from Claim 54 and Claims 57 and 58 depend from Claim 56. Claim 54 is directed to a composition that includes a defined genus of compounds and at least one additional agent for the treatment of breast cancer. Claim 56 is directed to a method for treating breast cancer using the genus of compounds defined in Claim 54.

As amended, Claim 54 recites a composition that includes a compound having the formula:



where Y is substituted or unsubstituted heterocyclyl;

R_1 is selected from the group consisting of H, C_1-C_6-alkyl, -COOH, and halo;

R_2 is substituted aryl; and

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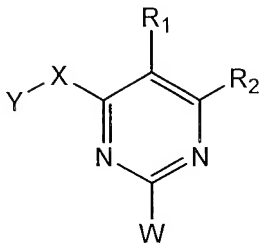
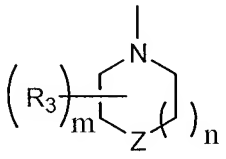
W is substituted or unsubstituted morpholino.

Withdrawal of the rejection is requested because, with the amendment of Claims 54 and 56, Claims 54-58 are entitled to the priority date of January 7, 2003, the filing date of U.S. Provisional Application No. 60/438,568 ("the '568 provisional application"), the benefit of which is claimed in the present application. The effective date of the Caine reference as prior art is October 15, 2003, and thus is not citable against claims supported by the '568 provisional application. A copy of the '568 provisional application is attached as **Exhibit A**.

The genus of compounds defined in Claims 54 and 56 are supported by the '568 provisional application. On page 3, line 5-page 4, line 4, the provisional application describes the genus of compounds defined in Claims 54 and 56 by describing compounds having the formula:



where W is



and where Z is -O-;

R_3 is absent;

X is a covalent bond;

Y is heterocyclyl and substituted heterocyclyl;

R_1 is hydrogen, halogen, carboxylic acid, and alkyl; and

R_2 is substituted aryl.

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The same description is also found at page 22, line 6-page 23, line 24 of the '568 provisional application. The '568 provisional also describes species of the genus. See, for example, page 57, compound 71; page 58, compounds 76, 80, and 81; page 59, compounds 82-88; page 65, compounds 124-128; and page 66, compound 131.

The '568 provisional application describes compositions of the compounds with other cytotoxic agents. See, for example, page 26, lines 16-18; and page 35, lines 20-24. Therefore, Claims 54 and 55 are supported by the '568 provisional application and are entitled to the priority of that application's filing date, January 7, 2003.

The '568 provisional application describes methods of treating cancer using the genus of compounds defined in Claim 56. See, for example, page 3, line 4; page 7, lines 1-3 and 14-15; page 26, lines 1-3 and 7-9; and page 32, lines 19-22. Therefore, Claims 56-58 are supported by the '568 provisional application and are entitled to the priority of that application's filing date, January 7, 2003.

Because the Caine reference has a publication date of October 15, 2003, which is later than January 7, 2003, the priority date for Claims 54-58, the reference is not properly citable against Claims 54-58. Withdrawal of the rejection is respectfully requested.

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CONCLUSION

In view of the above amendments and foregoing remarks, applicants believe that Claims 1-27, 31, 32, 37-43, 45, 46, and 54-58 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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EXHIBIT A

SMALL MOLECULE PI 3-KINASE INHIBITORS AND METHODS OF THEIR USE

FIELD OF THE INVENTION

This invention pertains generally to the treatment of diseases, such as cancer, characterized by the abnormal activity of growth factors, protein serine/threonine kinases, and phospholipid kinases. In other aspects, the present invention provides small molecule inhibitors of phosphotidylinositol (PI) 3-kinase, pharmaceutical formulations containing such inhibitors, methods of treating patients with such pharmaceutical formulations, and to methods of preparing such pharmaceutical formulations and inhibitors.

BACKGROUND OF THE INVENTION

Phosphotidylinositol 3-kinase (PI3K) is both a phospholipid kinase, and a protein serine/threonine kinase as described in Carpenter *et al, Mol. Cell. Biol. 13:*1657-1665 (1993). PI3K is an enzyme stimulated by growth factors that is responsible for phosphorylating phosphotidylinositol (PI) at the D-3' position of the inositol ring as described in Whitman *et al, Nature 332:*644-646 (1988). PI3K association with Src-like or receptor tyrosine kinases also implicates PI3K in the oncogenic or mitogenic responses induced by these protein

kinases, as described in Cantley *et al, Cell 64:*281-302 (1991), Escobedo and Williams, *Nature 335:*85-87 (1988), and Fantl *et al, Cell 69:*413-423 (1992).

Previously, studies to elucidate the downstream effects of PI 3-kinase activation have been conducted with receptor mutants constructed to alter the signal transduction of PI3K, or by constructing mutant oncogenes to study a PI3K inducible oncogenic response. The failure of receptor mutants of platelet derived growth factor (PDGF) receptor to activate PI3K has been correlated with deficiency of the receptor mutants in triggering a mitogenic response. Similarly, mutants of certain oncogenes have failed to trigger the oncogenic transformation inducible by the parent oncogene. A method was subsequently constructed to facilitate downstream effects of PI3K directly, without growth factor activation to determine whether PI3K was distinctly involved oncogenesis and mitogenesis. The results elucidated that PI3K can be directly or indirectly responsible for many cellular processes, such as mitogenesis and oncogenesis, as well as histamine secretion, neutrophil activation, platelet activation, cell migration, glucose transport, antilipolysis, and vesicle sorting.

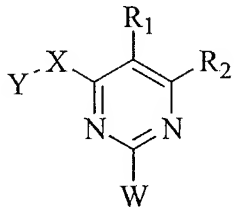
With the many regulatory responses associated with PI3-kinase, which is known to be involved in signal cascades involving other well known oncogenic proteins, such as receptor tyrosine kinases (e.g., VEGF-RTK), it would be highly desirable to produce small molecules capable of modulating, e.g. inhibiting, the activity of PI3-kinase.

It is an object of this invention to provide potent inhibitors of PI3K. It is further an object of the instant invention to provide compounds alone or in combination with other known agents to modulate cellular proliferation in patients in need thereof. Additionally, it is an object of this invention to provide medicaments for use in the treatment cancer.

SUMMARY OF THE INVENTION

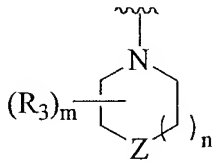
The present invention provides novel pyrimidine based compounds, pharmaceutical formulations comprising the compounds, methods of inhibiting phosphotidylinositol 3-kinase (PI3K), and methods of treating cancer.

In one embodiment, the present invention provides compounds of the following formula (I):



I

wherein W is:



wherein Z is selected from the group consisting of -CH_2-, -NH-, -O-, -S-, and –NR_6-, where R_6 is an alkyl or substituted alkyl group;

R_3 is absent or selected from the group consisting of alkyl, substituted alkyl, amino, alkylamino, aminoalkyl, dialkylamino, dialkylaminoalkyl, alkoxy, alkenyl, substituted alkenyl, alkynyl, carbonylamino, and alkoxycarbonyl; and

m and n are integers from 0-2;

X is a covalent bond or is selected from the group consisting of -CH_2-, -CHF-, -CF_2-, -NH-, -O-, -S-, and –NR_5-, where R_5 is an alkyl or substituted alkyl group;

Y is selected from the group consisting of heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

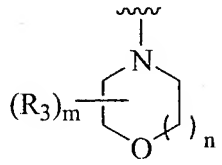
R_1 is selected from the group consisting of hydrogen, halogen, carboxylic acid, and alkyl; and

R_2 is selected from the group consisting of heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

the tautomers thereof;

and the pharmaceutically acceptable salts, esters, or prodrugs thereof.

In another aspect of the compound of formula (I), W is a morpholinyl group as shown below:



wherein, R_3, m, and n are as described above.

In another more particular embodiment of compound (I), W is an unsubstituted morpholinyl group.

In another more particular embodiment of compound (I), X is -NH-.

In another more particular embodiment of compound (I), Y is a heteroaryl or substituted heteroaryl group selected from pyridyl, and alkoxypyridyl.

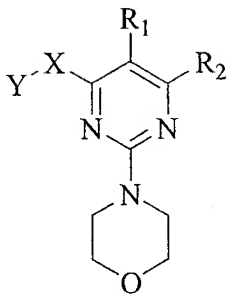
In another more particular embodiment of compound (I), R_1 is hydrogen.

In another more particular embodiment of compound (I), R_2 is an aryl or substituted aryl group.

In another more particular embodiment of compound (I), R_2 is selected from the group consisting of phenyl, phenol, aniline, hydroxybenzyl, phenylalkoxycarbonyl, phenylcarbonylalkoxy, phenylaminocarbonyl, and phenylcarbonylamino.

In another more particular embodiment of compound (I), R_3 is absent.

In one aspect of the invention, a compound of formula (II) is provided:



II

wherein X is selected from the group consisting of -NH-, -O-, and -S-;

Y is selected from the group consisting of heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R_1 is hydrogen, halogen, or a carboxylic acid group;

R_2 is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

the tautomers thereof;

and the pharmaceutically acceptable salts, esters, or prodrugs thereof.

In another aspect of the compound of formula (II), X is -NH-.

In another aspect of the compound of formula (II), Y is a heteroaryl or substituted heteroaryl group selected from pyridyl, and alkoxypyridyl.

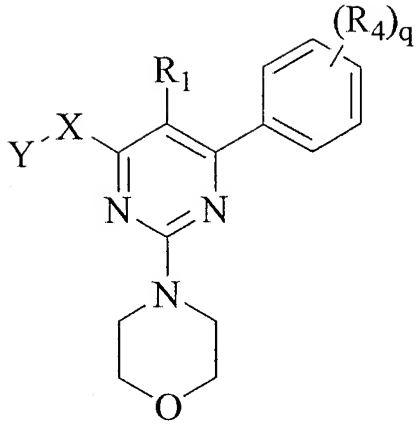
In another aspect of the compound of formula (II), R_1 is absent.

In another aspect of the compound of formula (II), R_2 is an aryl or substituted aryl group.

In another aspect of the compound of formula (II), R_2 is selected from the group consisting of phenyl, phenol, aniline, hydroxybenzyl, phenylalkoxycarbonyl, phenylcarbonylalkoxy, phenylaminocarbonyl, and phenylcarbonylamino.

In another aspect of the compound of formula (II), R_3 is absent.

In another aspect of the invention, compounds of formula (III) are provided:



III

wherein,

X is selected from the group consisting of -NH-, -O-, and -S-;

Y is selected from the group consisting of heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R_1 is hydrogen, halogen, or a carboxylic acid;

R_4 is independently selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, hydroxy, alkoxy, amino, alkylamino, aminoalkyl, dialkylamino, dialkylaminoalkyl, aryl, heteroaryl, heterocyclyl, carbonylamino, and alkoxycarbonyl; and

q is an integer from 1-5;

the tautomers thereof;

and the pharmaceutically acceptable salts, esters, or prodrugs thereof.

In another aspect of the compound of formula (III), X is -NH- and R_1 is hydrogen.

In another aspect of the compound of formula (III), R_4 is selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, hydroxy, alkoxy, amino, alkylamino, aminoalkyl, dialkylamino, dialkylaminoalkyl, carbonylamino, and alkoxycarbonyl.

A method of treating a patient in need of an inhibitor of phosphotidylinositol 3-kinase (PI3K) is provided which comprises administering an effective amount of the pharmaceutical formulation according to the present invention to a patient in need thereof.

Pharmaceutical formulations according to the present invention are provided which include any of the compounds described above in combination with a pharmaceutically acceptable carrier.

Further objects, features and advantages of the invention will be apparent from the following detailed description.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention provides novel compounds that act as inhibitors of serine/ threonine kinases, phospholipid kinases, and, more particularly, as inhibitors of phosphotidylinositol 3-kinase (PI3K) function. The compounds provided herein can be formulated into pharmaceutical formulations that are useful in treating patients with a need for an inhibitor of PI3K, especially, in particular embodiments, to provide compositions and methods for reducing cellular proliferation and in the treatment of cancer.

The following abbreviations and definitions are used throughout this application:

Abbreviation	Meaning
PI3K	phosphotidylinositol 3-kinase
AcOH	acetic acid
ATP:	adenosine triphosphate
BOC	tert-butoxycarbonyl
CPT 11	irinotecan
DIBAL-H	diisobutylaluminum hydride
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIEA	diisopropylethylamine
DMA:	N,N-Dimethylacetamide
DMF:	N,N-Dimethylformamide
DMSO	dimethyl sulfoxide
EDTA:	ethylene diamine tetraacetic acid

EtOAc:	ethyl acetate
EtOH:	ethanol
5-FU	5-fluourouracil
GCMS	Gas Chromatography / Mass Spectroscopy
HBTU:	O-benzotriazol-1-yl-N,N,N',N'-tetramethyl-uronium hexafluorophosphate
HPLC	High Performance Liquid Chromatography
IC_{50} value:	the concentration of an inhibitor that causes a 50 % reduction in a measured activity.
LCMS	Liquid Chromatography / Mass Spectroscopy
MeOH:	methanol
NMP:	N-methylpyrrolidone
NMR	nuclear magnetic resonance
Rt	room temperature (25°C)
THF:	tetrahydrofuran
TLC	thin-layer chromatography

The phrase "alkyl" refers to alkyl groups that do not contain heteroatoms. Thus the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C-(CH_2CH_3)_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(CH_2CH_3)CH-(CH_3)CH(CH_3)(CH_2CH_3)$, and others. The phrase also includes cyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl and such rings substituted with straight and branched chain alkyl groups as defined above. Thus the phrase alkyl groups include primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups.

Preferred alkyl groups include straight and branched chain alkyl groups and cyclic alkyl groups having 1 to 12 carbon atoms.

The phrase "substituted alkyl" refers to an alkyl group as defined above in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen and non-carbon atoms such as, but not limited to, a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, and ester groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as in trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. Substituted alkyl groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. Substituted alkyl groups further include alkyl groups in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to an aryl, heterocyclyl group, or cycloalkyl group. Preferred substituted alkyl groups include, among others, alkyl groups in which one or more bonds to a carbon or hydrogen atom is/are replaced by one or more bonds to fluorine atoms. Another preferred substituted alkyl group is the trifluoromethyl group and other alkyl groups that contain the trifluoromethyl group. Other preferred substituted alkyl groups include those in which one or more bonds to a carbon or hydrogen atom is replaced by a bond to an oxygen atom such that the substituted alkyl group contains a hydroxyl, alkoxy, or aryloxy group. Still other preferred substituted alkyl groups include alkyl groups that have an amine, or a substituted or unsubstituted alkylamine, dialkylamine, arylamine, (alkyl)(aryl)amine, diarylamine,

heterocyclylamine, diheterocyclylamine, (alkyl)(heterocyclyl)amine, or (aryl)(heterocyclyl)-amine group.

By halo is meant chloro, bromo, iodo, or fluoro or by halogen is meant chlorine, bromine, iodine or fluorine.

The phrase "alkenyl" refers to straight and branched chain and cyclic groups such as those described with respect to alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Examples include, but are not limited to vinyl, $-CH=C(H)(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=C(H)_2$, $-C(CH_3)=C(H)(CH_3)$, $-C(CH_2CH_3)=CH_2$, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others. The phrase "substituted alkenyl" has the same meaning with respect to alkenyl groups that substituted alkyl groups has with respect to unsubstituted alkyl groups. A substituted alkenyl group includes alkenyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon double bonded to another carbon and those in which one of the non-carbon or non-hydrogen atoms is bonded to a carbon not involved in a double bond to another carbon.

The phrase "alkynyl" refers to straight and branched chain groups such as those described with respect to alkyl groups as defined above, except that at least one triple bond exists between two carbon atoms. Examples include, but are not limited to $-C\equiv C(H)$, $-C\equiv C(CH_3)$, $-C\equiv C(CH_2CH_3)$, $-C(H_2)C\equiv C(H)$, $-C(H)_2C\equiv C(CH_3)$, and $-C(H)_2C\equiv C(CH_2CH_3)$ among others. The phrase "substituted alkynyl" has the same meaning with respect to alkynyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkynyl group includes alkynyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon triple bonded to another carbon and those in which a non-carbon or non-hydrogen atom is bonded to a carbon not involved in a triple bond to another carbon.

The phrase "heterocyclyl" refers to both aromatic and nonaromatic ring compounds including monocyclic, bicyclic, and polycyclic ring compounds such as, but not limited to, quinuclidinyl, containing 3 or more ring members of which one or more is a heteroatom such as, but not limited to, N, O, and S. Although the phrase "unsubstituted heterocyclyl" includes condensed heterocyclic rings such as benzimidazolyl, it does not include heterocyclyl groups that have other groups such as alkyl or halo groups bonded to one of the ring members as compounds such as 2-methylbenzimidazolyl are substituted heterocyclyl groups. Examples of heterocyclyl groups include, but are not limited to: unsaturated 3- to 8-membered rings containing 1 to 4 nitrogen atoms such as, but not limited to pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl etc.), tetrazolyl, (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.); saturated 3- to 8-membered rings containing 1 to 4 nitrogen atoms such as, but not limited to, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl; condensed unsaturated heterocyclic groups containing 1 to 4 nitrogen atoms such as, but not limited to, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl; unsaturated 3- to 8-membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.); saturated 3- to 8-membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, morpholinyl; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzoxazolyl, benzoxadiazolyl, benzoxazinyl (e.g. 2H-1,4-benzoxazinyl etc.); unsaturated 3- to 8-membered rings containing 1 to 3 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.); saturated 3- to 8-membered rings containing 1 to

2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolodinyl; saturated and unsaturated 3- to 8-membered rings containing 1 to 2 sulfur atoms such as, but not limited to, thienyl, dihydrodithienyl, dihydrodithionyl, tetrahydrothiophene, tetrahydrothiopyran; unsaturated condensed heterocyclic rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, benzothiazolyl, benzothiadiazolyl, benzothiazinyl (e.g. 2H-1,4-benzothiazinyl, etc.), dihydrobenzothiazinyl (e.g. 2H-3,4-dihydrobenzothiazinyl, etc.), unsaturated 3- to 8-membered rings containing oxygen atoms such as, but not limited to furyl; unsaturated condensed heterocyclic rings containing 1 to 2 oxygen atoms such as benzodioxolyl (e.g. 1,3-benzodioxoyl, etc.); unsaturated 3- to 8-membered rings containing an oxygen atom and 1 to 2 sulfur atoms such as, but not limited to, dihydrooxathienyl; saturated 3- to 8-membered rings containing 1 to 2 oxygen atoms and 1 to 2 sulfur atoms such as 1,4-oxathiane; unsaturated condensed rings containing 1 to 2 sulfur atoms such as benzothienyl, benzodithienyl; and unsaturated condensed heterocyclic rings containing an oxygen atom and 1 to 2 oxygen atoms such as benzoxathienyl. Heterocyclyl group also include those described above in which one or more S atoms in the ring is double-bonded to one or two oxygen atoms (sulfoxides and sulfones). For example, heterocyclyl groups include tetrahydrothiophene, tetrahydrothiophene oxide, and tetrahydrothiophene 1,1-dioxide. Preferred heterocyclyl groups contain 5 or 6 ring members. More preferred heterocyclyl groups include morpholine, piperazine, piperidine, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiomorpholine, thiomorpholine in which the S atom of the thiomorpholine is bonded to one or more O atoms, pyrrole, homopiperazine, oxazolidin-2-one, pyrrolidin-2-one, oxazole, quinuclidine, thiazole, isoxazole, furan, and tetrahydrofuran.

The phrase "substituted heterocyclyl" refers to a heterocyclyl group as defined above in which one of the ring members is bonded to a non-hydrogen atom such as described above

with respect to substituted alkyl groups and substituted aryl groups. Examples, include, but are not limited to, 2-methylbenzimidazolyl, 5-methylbenzimidazolyl, 5-chlorobenzthiazolyl, 1-methyl piperazinyl, and 2-chloropyridyl among others.

The phrase "aryl" refers to aryl groups that do not contain heteroatoms. Thus the phrase includes, but is not limited to, groups such as phenyl, biphenyl, anthracenyl, naphthenyl by way of example. Although the phrase "unsubstituted aryl" includes groups containing condensed rings such as naphthalene, it does not include aryl groups that have other groups such as alkyl or halo groups bonded to one of the ring members, as aryl groups such as tolyl are considered herein to be substituted aryl groups as described below. A preferred unsubstituted aryl group is phenyl. Unsubstituted aryl groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound, however.

The phrase "substituted aryl group" has the same meaning with respect to unsubstituted aryl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. However, a substituted aryl group also includes aryl groups in which one of the aromatic carbons is bonded to one of the non-carbon or non-hydrogen atoms described above and also includes aryl groups in which one or more aromatic carbons of the aryl group is bonded to a substituted and/or unsubstituted alkyl, alkenyl, or alkynyl group as defined herein. This includes bonding arrangements in which two carbon atoms of an aryl group are bonded to two atoms of an alkyl, alkenyl, or alkynyl group to define a fused ring system (e.g. dihydronaphthyl or tetrahydronaphthyl). Thus, the phrase "substituted aryl" includes, but is not limited to tolyl, and hydroxyphenyl among others.

The term "heteroaryl", as used herein, refers to a cyclic or bicyclic aromatic radical having from five to ten ring atoms in each ring of which one atom of the cyclic or bicyclic ring is selected from S, O and N; zero, one or two ring atoms are additional heteroatoms

independently selected from S, O and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and naphthyridinyl, and the like.

The term "substituted heteroaryl" as used herein refers to a heteroaryl group as defined herein substituted by independent replacement of one, two or three of the hydrogen atoms thereon with Cl, Br, F, I, -OH, -CN, C_1-C_3-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy substituted with aryl, haloalkyl, thioalkoxy, amino, alkylamino, dialkylamino, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, any one substituent may be an aryl, heteroaryl, or heterocycloalkyl group.

The term "biaryl" refers to a group or substituent to which two aryl groups, which are not condensed to each other, are bound. Exemplary biaryl compounds include, for example, phenylbenzene, diphenyldiazene, 4-methylthio-1-phenylbenzene, phenoxybenzene, (2-phenylethynyl)benzene, diphenyl ketone, (4-phenylbuta-1,3-diynyl)benzene, phenyl-benzylamine, (phenylmethoxy)benzene, and the like. Preferred optionally substituted biaryl groups include: 2-(phenylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 1,4-diphenyl-benzene, N-[4-(2-phenylethynyl)phenyl]-2-[benzylamino]acetamide, 2-amino-N-[4-(2-phenylethynyl)phenyl]propanamide, 2-amino-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(cyclopropylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(ethylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-[(2-methylpropyl)amino]-N-[4-(2-phenylethynyl)-phenyl]acetamide, 5-phenyl-2H-benzo[d]1,3-dioxolene, 2-chloro-1-methoxy-4-phenyl-benzene, 2-[(imidazolylmethyl)amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 4-phenyl-1-phenoxybenzene, N-(2-aminoethyl)[4-(2-phenylethynyl)phenyl]carboxamide, 2-{[(4-fluorophenyl)methyl]amino}-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-{[(4-methyl-

phenyl)methyl]amino}-N-[4-(2-phenylethynyl)phenyl]acetamide, 4-phenyl-1-(trifluoromethyl)benzene, 1-butyl-4-phenylbenzene, 2-(cyclohexylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(ethylmethylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(butylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(4-pyridylamino)acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(quinuclidin-3-ylamino)-acetamide, N-[4-(2-phenylethynyl)phenyl]pyrrolidin-2-ylcarboxamide, 2-amino-3-methyl-N-[4-(2-phenylethynyl)phenyl]butanamide, 4-(4-phenylbuta-1,3-diynyl)phenylamine, 2-(dimethylamino)-N-[4-(4-phenylbuta-1,3-diynyl)phenyl]acetamide, 2-(ethylamino)-N-[4-(4-phenylbuta-1,3-diynyl)phenyl]acetamide, 4-ethyl-1-phenylbenzene, 1-[4-(2-phenylethynyl)-phenyl]ethan-1-one, N-(1-carbamoyl-2-hydroxypropyl)[4-(4-phenylbuta-1,3-diynyl)phenyl]-carboxamide, N-[4-(2-phenylethynyl)phenyl]propanamide, 4-methoxyphenyl phenyl ketone, phenyl-N-benzamide, (tert-butoxy)-N-[(4-phenylphenyl)methyl]carboxamide, 2-(3-phenyl-phenoxy)ethanehydroxamic acid, 3-phenylphenyl propanoate, 1-(4-ethoxyphenyl)-4-methoxybenzene, and [4-(2-phenylethynyl)phenyl]pyrrole.

The term "heteroarylaryl" refers to a biaryl group where one of the aryl groups is a heteroaryl group. Exemplary heteroarylaryl groups include, for example, 2-phenylpyridine, phenylpyrrole, 3-(2-phenylethynyl)pyridine, phenylpyrazole, 5-(2-phenylethynyl)-1,3-dihydropyrimidine-2,4-dione, 4-phenyl-1,2,3-thiadiazole, 2-(2-phenylethynyl)pyrazine, 2-phenylthiophene, phenylimidazole, 3-(2-piperazinylphenyl)furan, 3-(2,4-dichlorophenyl)-4-methylpyrrole, and the like. Preferred optionally substituted heteroarylaryl groups include: 5-(2-phenylethynyl)pyrimidine-2-ylamine, 1-methoxy-4-(2-thienyl)benzene, 1-methoxy-3-(2-thienyl)benzene, 5-methyl-2-phenylpyridine, 5-methyl-3-phenylisoxazole, 2-[3-(trifluoromethyl)phenyl]furan, 3-fluoro-5-(2-furyl)-2-methoxy-1-prop-2-enylbenzene, (hydroxyimino)(5-phenyl(2-thienyl))methane, 5-[(4-methylpiperazinyl)methyl]-2-phenylthiophene, 2-(4-ethylphenyl)thiophene, 4-methylthio-1-(2-thienyl)benzene, 2-(3-

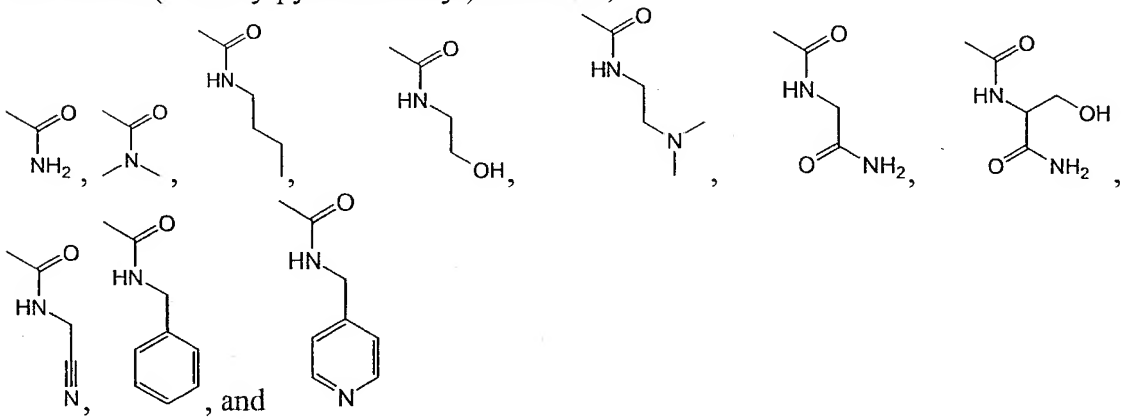
nitrophenyl)thiophene, (tert-butoxy)-N-[(5-phenyl(3-pyridyl))methyl]carboxamide, hydroxy-N-[(5-phenyl(3-pyridyl))methyl]amide, 2-(phenylmethylthio)pyridine, and benzylimidazole.

The term "heteroarylheteroaryl" refers to a biaryl group where both of the aryl groups are heteroaryl groups. Exemplary heteroarylheteroaryl groups include, for example, 3-pyridylimidazole, 2-imidazolylpyrazine, and the like. Preferred optionally substituted heteroarylheteroaryl groups include: 2-(4-piperazinyl-3-pyridyl)furan, diethyl(3-pyrazin-2-yl(4-pyridyl))amine, and dimethyl{2-[2-(5-methylpyrazin-2-yl)ethynyl](4-pyridyl)}amine.

"Optionally substituted" refers to the optional replacement of hydrogen with one or more monovalent or divalent radicals. Optionally substituted groups include those described herein, for each group in which a distinct definition for substitution is supplied. Additionally, suitable substitution groups include, for example, hydroxyl, nitro, amino, imino, cyano, halo, thio, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, substituted alkyl, halologweralkyl, loweralkoxy, halologweralkoxy, loweralkoxyalkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, benzyl, pyridyl, pyrazolyl, pyrrole, thiophene, imidazolyl, and the like.

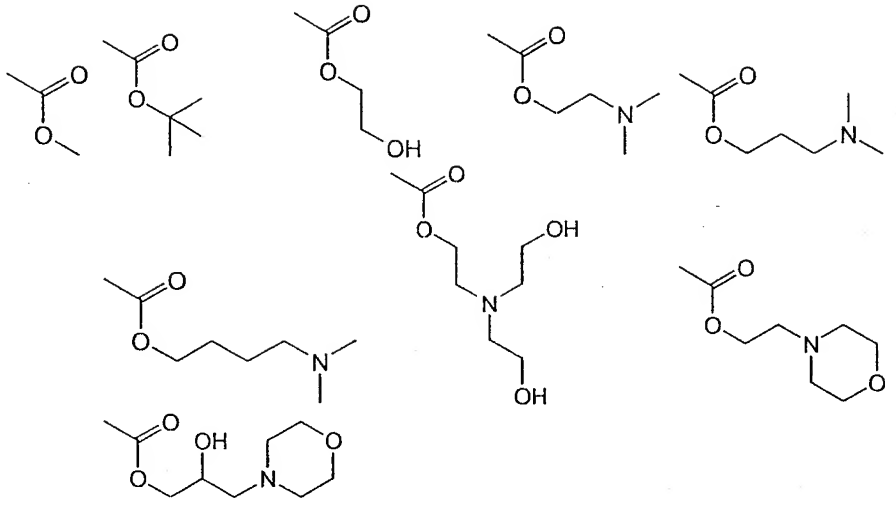
Representative substituted aminocarbonyl groups include, for example, those shown below. These can be further substituted by heterocyclyl groups and heteroaryl groups as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein. Preferred aminocarbonyl groups include: N-(2-cyanoethyl)carboxamide, N-(3-methoxypropyl)carboxamide, N-cyclopropylcarboxamide, N-(2-hydroxy-isopropyl)carboxamide, methyl 2-carbonylamino-3-hydroxypropanoate, N-(2-hydroxypropyl)carboxamide, N-(2-hydroxy-isopropyl)carboxamide, N-[2-hydroxy-1-(hydroxymethyl)ethyl]carboxamide, N-(2-carbonylaminoethyl)acetamide, N-(2-(2-pyridyl)ethyl)carboxamide, N-(2-pyridylmethyl)carboxamide, N-(oxolan-2-ylmethyl)-

carboxamide, N-(4-hydroxypyrrolidin-2-yl)carboxamide, N-[2-(2-hydroxyethoxy)ethyl]-carboxamide, N-(4-hydroxycyclohexyl)carboxamide, N-[2-(2-oxo-4-imidazolinyl)ethyl]-carboxamide, N-(carbonylaminomethyl)acetamide, N-(3-pyrrolidinylpropyl)carboxamide, N-[1-(carbonylaminomethyl)pyrrolidin-3-yl]acetamide, N-(2-morpholin-4-ylethyl)-carboxamide, N-[3-(2-oxopyrrolidinyl)propyl]carboxamide, 4-methyl-2-oxopiperazine-carbaldehyde, N-(2-hydroxy-3-pyrrolidinylpropyl)carboxamide, N-(2-hydroxy-3-morpholin-4-ylpropyl)carboxamide, N-{2-[(5-cyano-2-pyridyl)amino]ethyl}carboxamide, 3-(dimethyl-amino)pyrrolidinecarbaldehyde, N-[(5-methylpyrazin-2-yl)methyl]carboxamide, 2,2,2-trifluoro-N-(1-formylpyrrolidin-3-yl)acetamide,



, and

Representative substituted alkoxycarbonyl groups include, for example, those shown below. These alkoxycarbonyl groups can be further substituted as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.



The term "protected" with respect to hydroxyl groups, amine groups, and sulfhydryl groups refers to forms of these functionalities which are protected from undesirable reaction with a protecting group known to those skilled in the art such as those set forth in *Protective Groups in Organic Synthesis*, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999) which can be added or removed using the procedures set forth therein. Examples of protected hydroxyl groups include, but are not limited to, silyl ethers such as those obtained by reaction of a hydroxyl group with a reagent such as, but not limited to, t-butyldimethyl-chlorosilane, trimethylchlorosilane, triisopropylchlorosilane, triethylchlorosilane; substituted methyl and ethyl ethers such as, but not limited to methoxymethyl ether, methythiomethyl ether, benzyloxymethyl ether, t-butoxymethyl ether, 2-methoxyethoxymethyl ether, tetrahydropyranyl ethers, 1-ethoxyethyl ether, allyl ether, benzyl ether; esters such as, but not limited to, benzoylformate, formate, acetate, trichloroacetate, and trifluoracetate. Examples of protected amine groups include, but are not limited to, amides such as, formamide, acetamide, trifluoroacetamide, and benzamide; imides, such as phthalimide, and dithiosuccinimide; and others. Examples of protected sulfhydryl groups include, but are not limited to, thioethers such as S-benzyl thioether, and

S-4-picolyl thioether; substituted S-methyl derivatives such as hemithio, dithio and aminothio acetals; and others.

A "pharmaceutically acceptable salt" includes a salt with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. As salts of inorganic bases, the invention includes, for example, alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. As salts of organic bases, the invention includes, for example, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. As salts of inorganic acids, the instant invention includes, for example, hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. As salts of organic acids, the instant invention includes, for example, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. As salts of basic amino acids, the instant invention includes, for example, arginine, lysine and ornithine. Acidic amino acids include, for example, aspartic acid and glutamic acid.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Representative examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals

with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

As used herein, "limit", "treat" and "treatment" are interchangeable terms as are "limiting" and "treating" and, as used herein, include preventative (e.g., prophylactic) and palliative treatment or the act of providing preventative or palliative treatment.

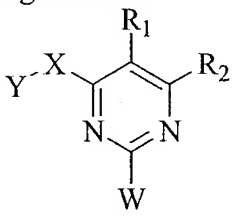
"Treating" within the context of the instant invention, means an alleviation of symptoms associated with a disorder or disease, or halt of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder. For example, within the context of treating patients in need of an inhibitor of PI3K, successful treatment may include a reduction in the proliferation of capillaries feeding a tumor or diseased tissue, an alleviation of symptoms related to a cancerous growth or tumor, proliferation of capillaries, or diseased tissue, a halting in capillary proliferation, or a halting in the progression of a disease such as cancer or in the growth of cancerous cells. Treatment may also include administering the pharmaceutical formulations of the present invention in combination with other therapies. For example, the compounds and pharmaceutical formulations of the present invention may be administered before, during, or after surgical procedure and/or radiation therapy. The compounds of the invention can also be administered in conjunction with other anti-cancer drugs including those used in antisense and gene therapy.

The PI3K inhibitors of this invention, as described herein, can be administered in the form of acid addition salts. The salts are conveniently formed by reacting a compound, if basic, with a suitable acid, such as have been described above. The salts are quickly formed in high yields at moderate temperatures, and often are prepared by merely isolating the compound from a suitable acidic wash as the final step of the synthesis. The salt-forming acid is dissolved in an appropriate organic solvent, or aqueous organic solvent, such as an alkanol, ketone or ester. On the other hand, if the compound of this invention is desired in the free base form, it is isolated from a basic final wash step, according to the usual practice. A preferred technique for preparing hydrochlorides is to dissolve the free base in a suitable solvent and dry the solution thoroughly, as over molecular sieves, before bubbling hydrogen chloride gas through it. It will also be recognized that it is possible to administer amorphous forms of the PI3K inhibitors.

The subject invention also includes isotopically-labeled PI3K inhibitors, which are structurally identical to those disclosed above, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds and of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further,

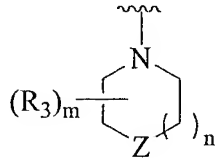
substitution with heavier isotopes such as deuterium, i.e., ^2H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out known or referenced procedures and by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Generally, the invention provides compounds having the structure I. The invention also provides tautomers of the compounds, pharmaceutically acceptable salts, esters and prodrugs of the compounds, and pharmaceutically acceptable salts, esters and prodrugs of the tautomers. Structure I has the following formula:



I

wherein W is:



wherein Z is selected from the group consisting of $-CH_2-$, -NH-, -O-, -S-, and $-NR_6-$, where R_6 is an alkyl or substituted alkyl group;

R_3 is absent or selected from the group consisting of alkyl, substituted alkyl, amino, alkylamino, aminoalkyl, dialkylamino, dialkylaminoalkyl, alkoxy, alkenyl, substituted alkenyl, alkynyl, carbonylamino, and alkoxycarbonyl; and

m and n are integers from 0-2;

X is a covalent bond or is selected from the group consisting of $-CH_2-$, -CHF-, $-CF_2-$, -NH-, -O-, -S-, and $-NR_5-$, where R_5 is an alkyl or substituted alkyl group;

Y is selected from the group consisting of heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

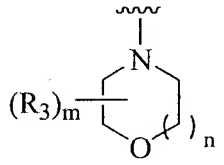
R_1 is selected from the group consisting of hydrogen, halogen, carboxylic acid, and alkyl; and

R_2 is selected from the group consisting of heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

the tautomers thereof; and

the pharmaceutically acceptable salts, esters, or prodrugs thereof.

In another aspect of the compound of formula (I), X is a covalent bond and Y is a morpholinyl group as shown below:



wherein, R_3, m, and n are as described above.

In another more particular embodiment of compound (I), X is a covalent bond and Y is an unsubstituted morpholinyl group.

In another more particular embodiment of compound (I), X is -NH-.

In another more particular embodiment of compound (I), Y is a heteroaryl or substituted heteroaryl group selected from pyridyl and alkoxypyridyl.

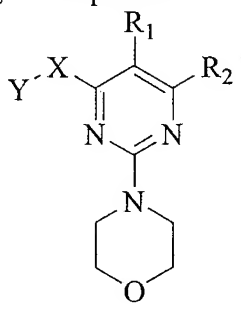
In another more particular embodiment of compound (I), R_1 is hydrogen.

In another more particular embodiment of compound (I), R_2 is an aryl or substituted aryl group.

In another more particular embodiment of compound (I), R_2 is selected from the group consisting of phenyl, phenol, aniline, hydroxybenzyl, phenylalkoxycarbonyl, phenylcarbonylalkoxy, phenylaminocarbonyl, and phenylcarbonylamino.

In another more particular embodiment of compound (I), R_3 is absent.

In one aspect of the invention, a compound of formula (II) is provided:



II

wherein, X is selected from the group consisting of -NH-, -O-, and -S-;

Y is selected from the group consisting of heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R_1 is hydrogen, halogen, or a carboxylic acid group;

R_2 is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

the tautomers thereof;

and the pharmaceutically acceptable salts, esters, or prodrugs thereof.

In another aspect of the compound of formula (II), X is -NH-.

In another aspect of the compound of formula (II), Y is a heteroaryl or substituted heteroaryl group selected from pyridyl and alkoxypyridyl.

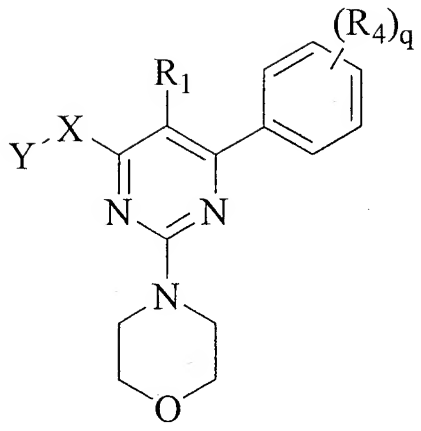
In another aspect of the compound of formula (II), R_1 is hydrogen.

In another aspect of the compound of formula (II), R_2 is an aryl or substituted aryl group.

In another aspect of the compound of formula (II), R_2 is selected from the group consisting of phenyl, phenol, aniline, hydroxybenzyl, phenylalkoxycarbonyl, phenylcarbonylalkoxy, phenylaminocarbonyl, and phenylcarbonylamino.

In another aspect of the compound of formula (II), R_3 is absent.

In another aspect of the invention, compounds of formula (III) are provided:



III

wherein,

X is selected from the group consisting of -NH-, -O-, and -S-;

Y is selected from the group consisting of heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R_1 is hydrogen, halogen, or a carboxylic acid;

R_4 is independently selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, hydroxy, alkoxy, amino, alkylamino, aminoalkyl, dialkylamino, dialkylaminoalkyl, aryl, heteroaryl, heterocyclyl, carbonylamino, and alkoxycarbonyl;

q is an integer from 1-5.

the tautomers thereof;

and the pharmaceutically acceptable salts, esters, or prodrugs thereof.

In another aspect of the compound of formula (III), X is -NH- and R_1 is hydrogen.

In another aspect of the compound of formula (III), R_4 is selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, hydroxy, alkoxy, amino, alkylamino, aminoalkyl, dialkylamino, dialkylaminoalkyl, carbonylamino, and alkoxycarbonyl.

A method of treating a patient in need of an inhibitor of phosphotidylinositol 3-kinase (PI3K) is provided which comprises administering an effective amount of the pharmaceutical formulation according to the present invention to a patient in need thereof.

Pharmaceutical formulations according to the present invention are provided which include any of the compounds described above in combination with a pharmaceutically acceptable carrier.

A method for inhibiting tumor growth in a patient comprises administering an effective amount of the compound or a pharmaceutically acceptable salt thereof to a patient having a tumor.

A method for inhibiting the proliferation of capillaries in a patient comprises administering an effective amount of the compound or a pharmaceutically acceptable salt thereof according to a patient in need.

A method of preparing pharmaceutical formulations comprises mixing any of the above-described compounds with a pharmaceutically acceptable carrier and water or an aqueous solution.

Combinations of compounds of structure I, II, and III with other conventional cytotoxic agents, such as, for example, tamoxifen, CPT 11, 5-FU, and the like are considered to fall within the scope of this invention.

PHARMACEUTICAL COMPOSITIONS

Pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such

as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or as an oral or nasal spray, or a liquid aerosol or dry powder formulation for inhalation.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form may be accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations may also be prepared

by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, acetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in

the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be

required. Ophthalmic formulations, ear drops, and the like are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Compositions of the invention may also be formulated for delivery as a liquid aerosol or inhalable dry powder. Liquid aerosol formulations may be nebulized predominantly into particle sizes that can be delivered to the terminal and respiratory bronchioles.

Aerosolized formulations of the invention may be delivered using an aerosol forming device, such as a jet, vibrating porous plate or ultrasonic nebulizer, preferably selected to allow the formation of an aerosol particles having with a mass medium average diameter predominantly between 1 to 5 μ. Further, the formulation preferably has balanced osmolarity ionic strength and chloride concentration, and the smallest aerosolizable volume able to deliver effective dose of the compounds of the invention to the site of the infection. Additionally, the aerosolized formulation preferably does not impair negatively the functionality of the airways and does not cause undesirable side effects.

Aerosolization devices suitable for administration of aerosol formulations of the invention include, for example, jet, vibrating porous plate, ultrasonic nebulizers and energized dry powder inhalers, that are able to nebulize the formulation of the invention into aerosol particle size predominantly in the size range from 1-5 μ. Predominantly in this application means that at least 70% but preferably more than 90% of all generated aerosol particles are within 1-5 μ range. A jet nebulizer works by air pressure to break a liquid solution into aerosol droplets. Vibrating porous plate nebulizers work by using a sonic vacuum produced by a rapidly vibrating porous plate to extrude a solvent droplet through a

porous plate. An ultrasonic nebulizer works by a piezoelectric crystal that shears a liquid into small aerosol droplets. A variety of suitable devices are available, including, for example, AeroNeb™ and AeroDose™ vibrating porous plate nebulizers (AeroGen, Inc., Sunnyvale, California), Sidestream® nebulizers (Medic-Aid Ltd., West Sussex, England), Pari LC® and Pari LC Star® jet nebulizers (Pari Respiratory Equipment, Inc., Richmond, Virginia), and Aerosonic™ (DeVilbiss Medizinische Produkte (Deutschland) GmbH, Heiden, Germany) and UltraAire® (Omron Healthcare, Inc., Vernon Hills, Illinois) ultrasonic nebulizers.

Compounds of the invention may also be formulated for use as topical powders and sprays that can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

According to the methods of treatment of the present invention, tumor growth is reduced or prevented in a patient such as a human or lower mammal by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to treat tumor growth, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and

compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other mammal in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 2000 mg of the compound(s) of this invention per day in single or multiple doses.

Methods of formulation are well known in the art and are disclosed, for example, in Remington: *The Science and Practice of Pharmacy*, Mack Publishing Company, Easton, Pa., 19th Edition (1995). Pharmaceutical compositions for use in the present invention can be in the form of sterile, non-pyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art.

A "kit" as used in the instant application comprises a container for containing the pharmaceutical compositions and may also include divided containers such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a

paper or cardboard box, a glass or plastic bottle or jar, a resealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It maybe desirable to provide a written memory aid, where the written memory aid is of the type containing information and/or instructions for the physician, pharmacist or other

health care provider, or subject, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested or a card which contains the same type of information. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday,"... etc ... "Second Week, Monday, Tuesday, ..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. When the kit contains separate compositions, a daily dose of one or more compositions of the kit can consist of one tablet or capsule while a daily dose of another one or more compositions of the kit can consist of several tablets or capsules.

Another specific embodiment of a kit is a dispenser designed to dispense the daily doses one at a time in the order of their intended use. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter, which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

The kits of the present invention may also comprise, in addition to a PI3K inhibitor, one or more additional pharmaceutically active compounds. Preferably, the additional compound is another PI3K inhibitor or another compound useful to treat cancer, angiogenisis, or tumor growth. The additional compounds may be administered in the same dosage form as the PI3K inhibitor or in different dosage forms. Likewise, the additional compounds can be administered at the same time as the PI3K inhibitor or at different times.

All references and patents cited herein are incorporated by reference.

The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

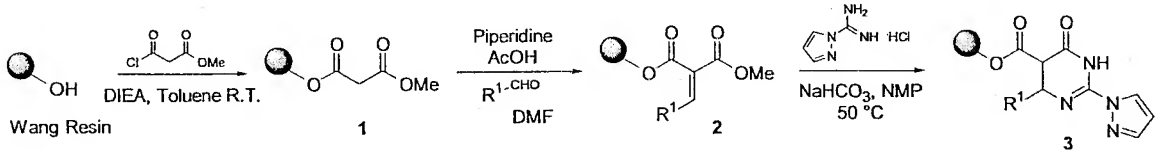
EXAMPLES

Experimental

Compounds of the invention may be generally prepared using procedures well known to those skilled in the art, for example in accordance with the following representative reaction schemes.

METHOD 1

Resin bound 2-(pyrazolo)trihydropyrimidin-4-one (3) (Step 1)

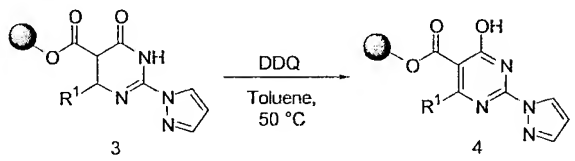


Scheme 1

Wang resin (1.0 g, 0.55 mmol, 1 eq) was suspended in toluene (10 mL) and DIEA (0.377 mL, 2.2 mmol, 4.0 eq) was added, followed by methyl malonyl chloride (0.236 mL, 2.2 mmol, 4.0 eq). The mixture was shaken overnight at room temperature. The resin was filtered and washed with CH_2Cl_2, MeOH, water, DMF, CH_2Cl_2 then dried to obtain resin bound methyl malonate **1**. Resin **1** (300 mg, 0.165 mmol, 1.0 eq) was suspended in a solution of piperidine (16.3 μL, 0.165 mmol, 1.0 eq) and acetic acid (9.4 μL, 0.165 mmol, 1.0 eq) in DMF (3 mL) and the aldehyde (10.0 eq) was added. The mixture was shaken at room temperature overnight. The resin was filtered, washed with DMF and CH_2Cl_2, then dried to give the resin bound α,β unsaturated diester **2**, which was used in the next step without analytics, since cleavage from the resin causes extensive decomposition. Resin **2** (300 mg, 0.165 mmol, 1.0 eq) was suspended in NMP (3 mL), and 1-H-pyrazole

carboxamidine hydrochloride (121 mg 0.825 mmol, 5.0 eq) was added, followed by $NaHCO_3$ (35 mg, 0.412 mmol, 2.5 eq). The reaction mixture was shaken overnight at 50 °C, then the resin was filtered, washed with DMF, water, MeOH, CH_2Cl_2 and dried, to obtain the desired resin bound 6-R^1-4-oxo-2-pyrazolyl-3,5,6-trihydropyrimidine-5-carboxylic acid **3**. An analytical sample of the cleaved product was obtained treating the resin with 95% TFA/H_2O for 1.5 h at room temperature, filtering and evaporating under reduced pressure.

Resin bound 2-pyrazolopyrimidinone (4) (Step 2)

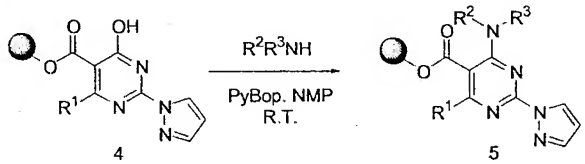


3 4

Step 2

Resin **3** (200 mg, 0.11 mmol, 1 eq) was suspended in 0.1 M solution of DDQ in toluene (2.5 mL, 253 mmol 2.3 eq) and the reaction mixture was shaken at 50°C overnight. The resin was filtered, washed with DMF, 20% aq AcOH, water, MeOH, CH_2Cl_2 and dried, to obtain the desired resin bound R^1-4-hydroxy-2-pyrazolylpyrimidine-5-carboxylic acid **4**. An analytical sample of the cleaved product was obtained treating the resin with 95% TFA/H_2O for 1.5 h at room temperature, filtering and evaporating under reduced pressure.

PyBop Mediated Substitution with Amines in the 4 Position, (Step 3)



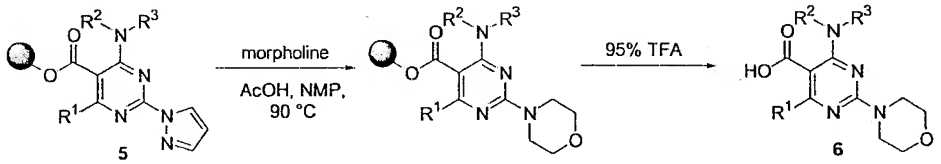
4 5

Step 3

A mixture of resin **4** (150 mg, 0.082 mmol, 1 eq), the amine of choice (10 eq), and PyBop (85 mg, 0.164 mmol, 2 eq) in NMP was shaken at room temperature overnight. The

resin was filtered, washed with DMF, MeOH, and CH_2Cl_2, and dried, to obtain the desired resin bound 6-R^1-4-aminoalkyl (or aryl)-2-pyrazolylpyrimidine-5-carboxylic acid **5**. An analytical sample of the cleaved product was obtained treating the resin 95% TFA/H_2O for 1.5 h at room temperature, filtering and evaporating under reduced pressure. .

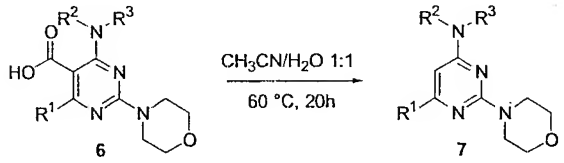
Sn_{Ar} with Morpholine in Position 2 (Step 4)



Step 4

Resin **5** (100 mg, 0.055 mmol, 1 eq) was suspended in NMP, and morpholine (144 µL, 144 mg, 1.65 mmol, 30 eq) was added, followed by acetic acid (31 µL, 33 mg, 0.55 mmol, 10 eq). The reaction mixture was shaken at 90°C overnight. The resin was filtered and washed with DMF, water, MeOH, CH_2Cl_2, then dried. The resin was treated with 95% TFA/H_2O for 1.5 h at room temperature. Filtration and evaporation under reduced pressure afforded 6-R^1-4-alkyl (or aryl)amino-2-morpholino pyrimidine-5-carboxylic acid **6**.

Decarboxylation (Step 5)



Step 5

The carboxylic acid **6** was dissolved in a mixture of acetonitrile and water (1:1, 2 mL) and the solution was heated at 60 °C overnight. The solution was cooled down to room temperature and then lyophilized. After purification by reverse phase liquid chromatography, the desired trisubstituted pyrimidine **7** was obtained as a solid.

Example 1

(Synthesis of 3-[6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol)

6-(3-hydroxyphenyl)-4-oxo-2-pyrazolyl-3,5,6-trihydropyrimidine-5-carboxylic acid

Wang resin (1.0 g, 0.55 mmol, 1 eq) was suspended in toluene (10 mL) and DIEA (0.377 mL, 2.2 mmol, 4.0 eq) was added, followed by methyl malonyl chloride (0.236 mL, 2.2 mmol, 4.0 eq). The mixture was shaken overnight at room temperature. The resin was filtered and washed with CH_2Cl_2, MeOH, water, DMF, CH_2Cl_2 then dried to obtain resin bound methyl malonate (1). Resin 1 (300 mg, 0.165 mmol, 1.0 eq) was suspended in a solution of piperidine (16.3 μL, 0.165 mmol, 1.0 eq) and acetic acid (9.4 μL, 0.165 mmol, 1.0 eq) and 3-hydroxybenzaldehyde (201 mg, 1.65 mmol, 10.0 eq) was added. The mixture was shaken at room temperature overnight. The resin was filtered, washed with DMF and CH_2Cl_2, dried, suspended in NMP, and 1-H-pyrazole carboxamidine hydrochloride (121 mg 0.825 mmol, 5.0 eq) was added, followed by $NaHCO_3$ (35 mg, 0.412 mmol, 2.5 eq). The reaction mixture was shaken overnight at 50 °C, then the resin was filtered, washed with DMF, water, MeOH, CH_2Cl_2 and dried. To obtain an analytical sample, 20 mg of the resin were treated with 95% TFA/H_2O for 1.5 h at room temperature. Filtration and evaporation under reduced pressure afforded 6-(3-hydroxyphenyl)-4-oxo-2-pyrazolyl-3,5,6-trihydropyrimidine-5-carboxylic acid.

HPLC (Buffer A: 0.1% TFA/H_2O; Buffer B: 0.1% TFA/CH_3CN; column: C18, 4.6x250mm; flow: 1mL/min; gradient: 2.1%, 5%-80% B in 36 min.): R_t= 14.70.

LC/MS (ion spray, 50 eV, *m/z*): 275 ($M+H_2O+H^+$)

4-hydroxy-6-(3-hydroxyphenyl)-2-pyrazolylpyrimidine-5-carboxylic acid

Resin bound 6-(3-hydroxyphenyl)-4-oxo-2-pyrazolyl-3,5,6-trihydropyrimidine-5-carboxylic acid (200 mg, 0.11 mmol, 1 eq) was suspended in 0.1 M solution of DDQ in toluene (2.5 mL, 253 mmol 2.3 eq) and the reaction mixture was shaken at 50 °C overnight. The resin was filtered, washed with DMF, 20% aq AcOH, water, MeOH, CH_2Cl_2 and dried. To obtain an analytical sample, 20 mg of the resin were treated with 95% TFA/H_2O for 1.5 h at room temperature. Filtration and evaporation under reduced pressure afforded 4-hydroxy-6-(3-hydroxyphenyl)-2-pyrazolylpyrimidine-5-carboxylic acid.

HPLC (Buffer A: 0.1% TFA/H_2O; Buffer B: 0.1% TFA/CH_3CN; column: C18, 4.6x250mm; flow: 1mL/min; gradient: 2.1%, 5%-80% B in 36 min.): R_t= 15.78.

LC-MS (ion spray, 50 eV, m/z): 299 ($M+H^+$)

Resin bound 6-(3-hydroxyphenyl)-4-(1H-indazol-5-ylamino)-2-pyrazolylpyrimidine-5-carboxylic acid

A mixture of resin bound 4-hydroxy-6-(3-hydroxyphenyl)-2-pyrazolylpyrimidine-5-carboxylic acid (150 mg, 0.082 mmol, 1 eq), 5-aminoindazole (110 mg, 0.82 mmol, 10 eq), and PyBop (85 mg, 0.164 mmol, 2 eq) in NMP was shaken at room temperature overnight. The resin was filtered, washed with DMF, MeOH, and CH_2Cl_2, and dried. To obtain an analytical sample, 20 mg of the resin were treated with 95% TFA/H_2O for 1.5 h at room temperature. Filtration and evaporation under reduced pressure afforded 6-(3-hydroxyphenyl)-4-(1H-indazol-5-ylamino)-2-pyrazolylpyrimidine-5-carboxylic acid.

HPLC (Buffer A: 0.1% TFA/H_2O; Buffer B: 0.1% TFA/CH_3CN; column: C18, 4.6x250mm; flow: 1mL/min; gradient: 2.1%, 5%-80% B in 36 min.): R_t= 20.72.

LC-MS (ion spray, 50 eV, m/z): 414 ($M+H^+$)

Resin bound 6-(3-hydroxyphenyl)-4-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidine-5-carboxylic acid

Resin bound 6-(3-hydroxyphenyl)-4-(1H-indazol-5-ylamino)-2-pyrazolylpyrimidine-5-carboxylic acid (100 mg, 0.055 mmol, 1 eq) was suspended in NMP, and morpholine (144 µL, 144 mg, 1.65 mmol, 30 eq) was added, followed by acetic acid (31 µL, 33mg, 0.55 mmol, 10 eq). The reaction mixture was shaken at 90 °C overnight. The resin was filtered and washed with DMF, water, MeOH, CH_2Cl_2, then dried. The resin was treated with 95% TFA/H_2O for 1.5 h at room temperature. Filtration and evaporation under reduced pressure afforded 6-(3-hydroxyphenyl)-4-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidine-5-carboxylic acid.

HPLC (Buffer A: 0.1% TFA/H_2O; Buffer B: 0.1% TFA/CH_3CN; column: C18, 4.6x250mm; flow: 1mL/min; gradient: 2.1%, 5%-80% B in 36 min.): R_t= 16.97.

LC-MS (ion spray, 50 eV, m/z): 433 ($M+H^+$)

3-[6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol

6-(3-hydroxyphenyl)-4-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidine-5-carboxylic acid was dissolved in a mixture of acetonitrile and water (1:1, 2 mL) and the solution was heated at 60 °C overnight. The solution was cooled down to room temperature and then lyophilized. After purification by reverse phase liquid chromatography (Buffer A: 0.1% TFA/H_2O; Buffer B: 0.1% TFA/CH_3CN, column: C18, 5µ, 10x50mm, gradient 5%B-95%B in 9 min) the Bis TFA salt of 3-[6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol was obtained as a pale yellow solid.

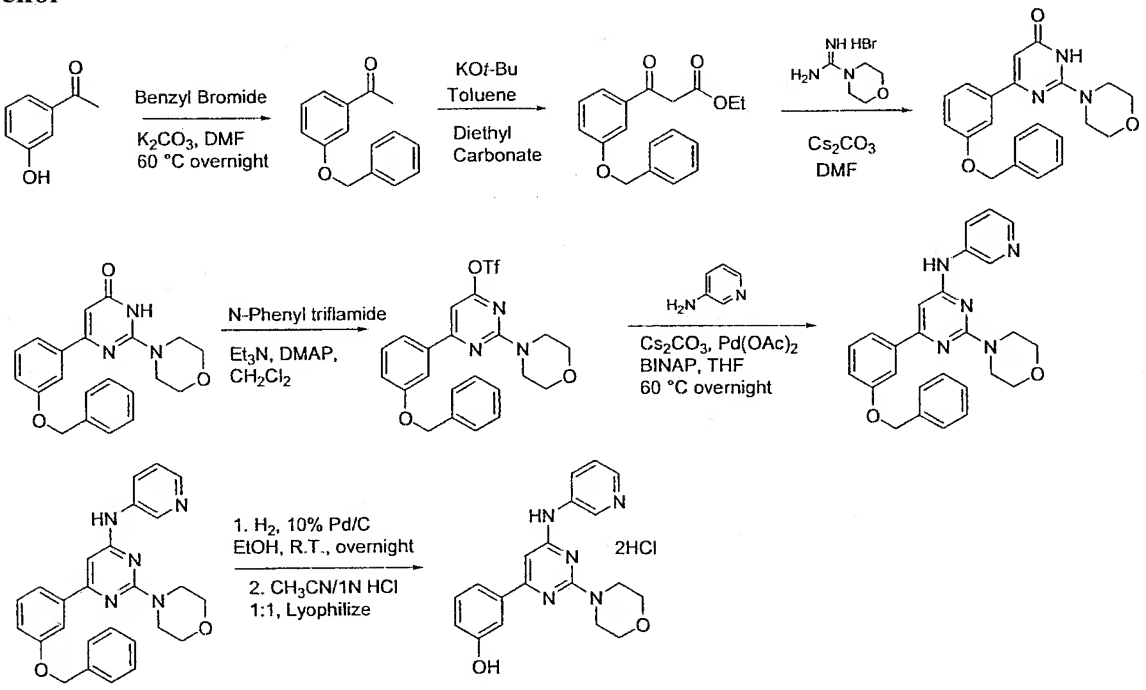
^{1}H-NMR (HCl salt, 60% CD_3CN/D_2O, 300 MHz): 8.09 (s, 1H), 8.03 (bs, 1H), 7.61 (1H, d, *J*= 8.7), 7.55 (bm, 1H), 7.38 (app. t, 1H, *J*= 7.8), 7.17 (bd, 1H, *J*= 7.8), 7.10 (bs, 1H), 7.06 (d, 1H, *J*= 8.7), 6.42 (bs, 1H), 3.75 (app. s, 8H).

HPLC (Buffer A: 0.1% TFA/H_2O; Buffer B: 0.1% TFA/CH_3CN; column: C18, 4.6x250mm; flow: 1mL/min; gradient: 2.1%, 5%-80% B in 36 min.): R_t= 18.17.

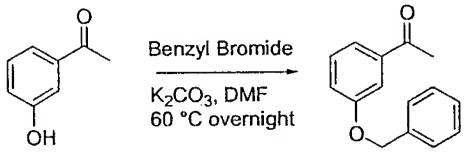
LC-MS (ion spray, 50 eV, m/z): 389 ($M+H^+$)

METHOD 2

Solution Phase Synthesis of 3-[2-Morpholin-4-yl-6-(3-pyridylamino)pyrimidin-4-yl]phenol



Step 1:



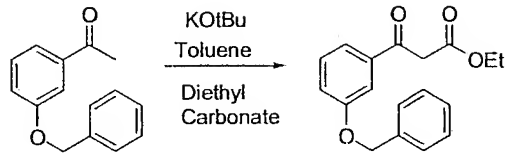
To a stirred solution of 3'-hydroxyacetophenone (1eq) and benzyl bromide (1.5 eq) in dry DMF under N_2, solid K_2CO_3 (2 eq) was added in one portion. The reaction mixture was stirred at 60° C for 3 days, then cooled down to room temperature. Most of the DMF was distilled off under reduced pressure. The residue was taken up in EtOAc and washed with 1N

HCl, H_2O, Brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded a brown oil which was about a 1:1 mixture of the starting material and the desired product. The latter was isolated by chromatography on silica gel (EtOAc/Hexanes, 1:1) affording the desired 3'-benzyloxy acetophenone (51%). See for example: Schmidhammer, H.; Brossi, A. *J. Org. Chem.* **1983**, *48*, 1469.

TLC (silica gel, Ethyl acetate/hexanes 1:2, vanillin stain): R_f= 0.58, orange brown (R_f starting material= 0.28)

^{1}H NMR ($CDCl_3$, 300MHz): 7.6-7.1 (9H, m), 5.11 (2H, s, CH_2Ph); 2.59 (3H, s, CH_3).

Step 2:



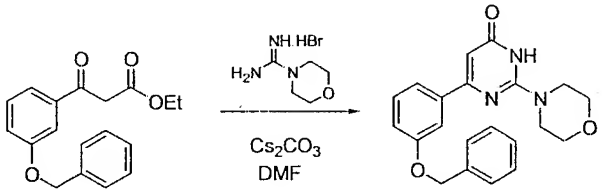
A round bottom flask, oven dried and kept under N_2 atmosphere, was charged with potassium *tert*-butoxide (2.2 eq) and dry toluene was added. The suspension was cooled down to 0 °C and a solution of 3'-benzyloxy acetophenone (1eq) and diethylcarbonate (2 eq) in toluene was added dropwise *via* a dropping funnel, with vigorous stirring. During the addition the temperature should not raise above 10 °C. After the end of the addition the reaction mixture was stirred at room temperature for 1h and then at 60 °C overnight. The reaction mixture was again cooled down to room temperature and quenched with a 1:10 mixture of acetic acid and water. The addition must be slow and occasional cooling might be necessary to keep the temperature below 20 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (x3). The organic extracts were collected and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure of crude ethyl 3-oxo-3-[3-(phenylmethoxy)phenyl]propanoate were obtained. The compound could be carried on to the next step without further purification.

TLC (silica gel, ethyl acetate/hexanes 1:5, vanillin stain): R_f= 0.26, faint orange brown

LC-MS (ion spray, 50 eV, m/z): 299 (M+ H^+)

^{1}H NMR ($CDCl_3$, 300MHz): 7.6-7.1 (9H, m); 5.10 (2H, bs, CH_2Ph); 4.21 (2H, q, *J*= 7.2 Hz OCH_2);3.96 (2H, s, $COCH_2$); 1.25 (3H, t, *J*= 7.2 Hz, CH_3)

Step 3:



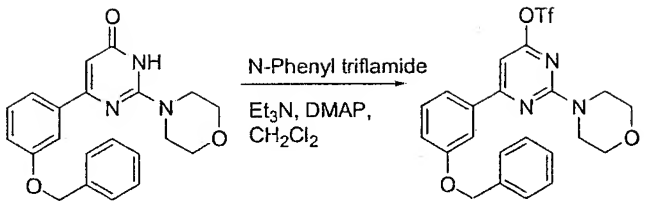
In a round bottom flask, oven dried and kept under N_2 atmosphere, Cs_2CO_3 (1.5 eq) was suspended in dry DMF. Morpholino formamidine hydrobromide (1.2 eq) was added, followed by ethyl 3-oxo-3-[3-(phenylmethoxy)phenyl] propanoate (1eq). The reaction mixture was stirred at 115 °C overnight, then cooled down to room temperature. The DMF was distilled off under reduced pressure and the residue was taken up in water, neutralizing with 5% HCl solution. The aqueous phase was then extracted with CH_2Cl_2 (x5). The organic extracts were collected and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the desired 2-morpholin-4-yl-6-[3-(phenylmethoxy) phenyl]-3-hydropyrimidin-4-one were obtained as an off white solid (60%). The crude is already pure enough for the next step, but it can be purified further by trituration with acetonitrile.

TLC (silica gel, CH_2Cl_2/MeOH 1:10): R_f= 0.32 (R_f of the starting material = 0.9).

LC-MS (ion spray, 50 eV, m/z): 364 (M+ H^+)

^{1}H NMR ($CDCl_3$, 300MHz): 7.65-7.3 (8H, m); 7.06 (1H, ddd, *J*= 8.4, 2.7, 0.9 Hz); 6.25 (1H, s); 5.13 (2H, s, CH_2Ph); 3.83 (8H, bs, morpholine).

Step 4:

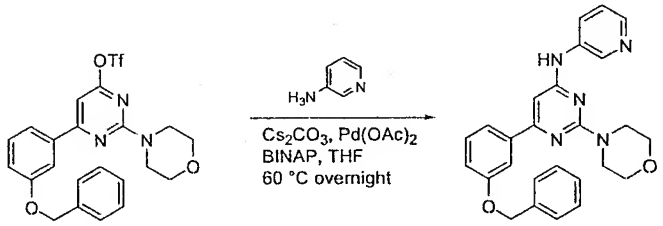


2-morpholin-4-yl-6-[3-(phenylmethoxy) phenyl]-3-hydropyrimidin-4-one (1eq) was dissolved in CH_2Cl_2 in a round bottom flask, oven dried and kept under N_2 atmosphere. The compound is not completely soluble. Triethylamine was added (1.4 eq) followed by N-Phenyl trifluoromethanesulfonimide (1.2 eq) and DMAP (10 mol%). The reaction mixture was stirred at room temperature overnight, obtaining a bright orange solution. The solvent was evaporated under reduced pressure and the residue purified by chromatography on silica gel (ethyl acetate/hexanes 1:5), obtaining (99%) the desired 2-morpholin-4-yl-6-[3-(phenylmethoxy)phenyl]pyrimidin-4-yl (trifluoromethyl) sulfonate

TLC (silica gel, EtOAc/Hexanes 1:5): R_f= 0.31

^{1}H NMR ($CDCl_3$, 300MHz): 7.64 (1H, dd, *J*=2.4, 1.5 Hz); 7.55 (1H, app. dt, *J*= 7.8, 1.2 Hz); 7.2-7.3 (6H, m); 7.12 (1H, ddd, *J*= 8.4, 2.4, 0.9 Hz); 6.66 (1H, s, pyrimidine CH), 5.14 (2H, s, CH_2Ph), 3.86 (4H, bm, morpholine); 3.79 (4H, m, morpholine).

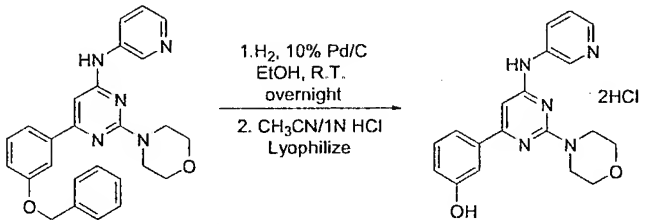
Step 5:



A round bottom flask, oven dried and kept under N_2 atmosphere was charged with Cs_2CO_3 (1.4 eq), $Pd(OAc)_2$ (5 mol%), and S-(-)-BINAP (1.5 x mol of Pd catalyst). The flask was purged with N_2 for about 5-10 min and a solution of 2-morpholin-4-yl-6-[3-(phenylmethoxy)phenyl]pyrimidin-4-yl (trifluoromethyl) sulfonate (1eq) in dry THF (20 mL)

was added via a syringe, followed by 3-aminopyridine (2 eq, see note 1) in one portion. The flask was equipped with a reflux condenser, purged again with N_2 for 5 min and the reaction mixture was refluxed overnight. An efficient stirring is very important. The reaction mixture was cooled down to room temperature and the solvent was evaporated under reduced pressure. The residue was washed with water (x2) and triturated with methanol to afford the desired {2-morpholin-4-yl-6-[3-(phenylmethoxy)phenyl]pyrimidin-4-yl}-3-pyridylamine.

Step 6:



{2-Morpholin-4-yl-6-[3-(phenylmethoxy)phenyl]pyrimidin-4-yl}-3-pyridylamine (1eq, see note 1) is suspended in ethanol in a round bottom flask, purged with N_2. 10% Pd/C (20% wt) was added. The flask was evacuated and filled up with H_2 (contained in a balloon) for five times, then the reaction mixture was stirred under H_2 for 20 h. The catalyst was filtered off through a pad of celite washing thoroughly with EtOH, MeOH, CH_2Cl_2, and acetonitrile (almost one liter of the mixture of solvents was used to ensure the complete solubilization of the product). The solvent was evaporated under reduced pressure and the residue purified by reverse phase chromatography (Buffer A: 0.1% TFA in H_2O, Buffer B: 0.1% TFA in CH_3CN; Column: Waters, C18, 47x300 mm; gradient: 1.1%, 10%-60%B in 45 min). The free base thus obtained was lyophilized from a 1:1 mixture of acetonitrile and 1N HCl, obtaining the desired 3-[2-morpholin-4-yl-6-(3-pyridylamino)pyrimidin-4-yl]phenol as the bis HCl salt. The spectral data are the following:

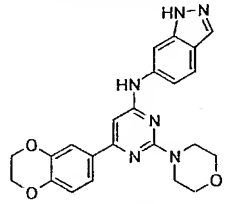
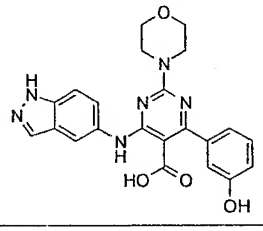
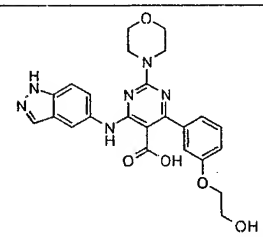
HPLC: (Buffer A: 0.1% TFA in H_2O, Buffer B: 0.1% TFA in CH_3CN; Column: Waters, C18, 4.6x250 mm; gradient: 4.2%, 5%-80%B in 18 min) R_t= 4.47

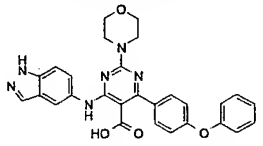
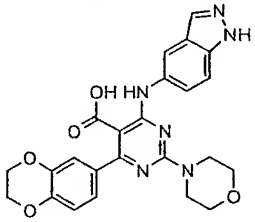
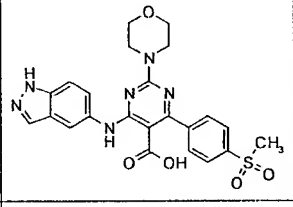
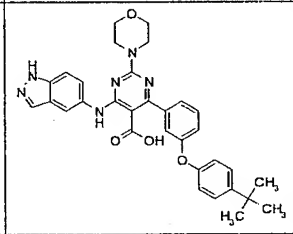
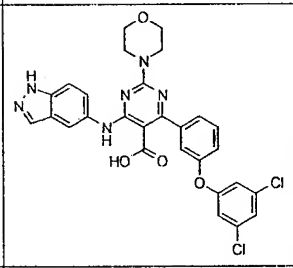
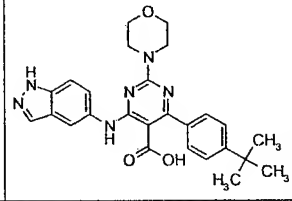
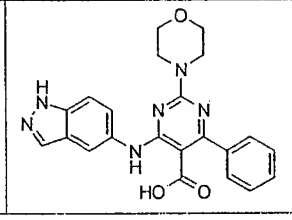
LC-MS (ion spray, 50 eV, m/z): 350 ($M+ H^+$)

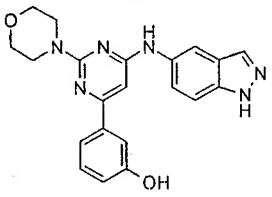
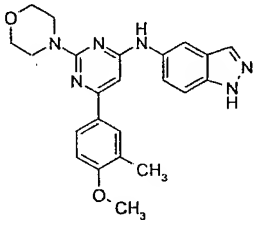
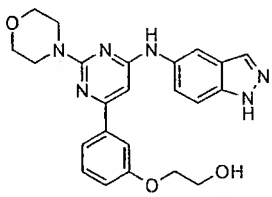
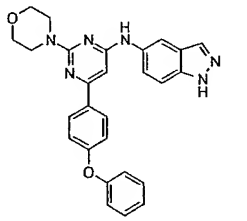
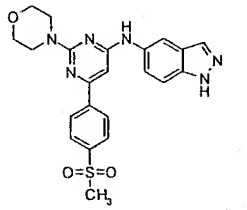
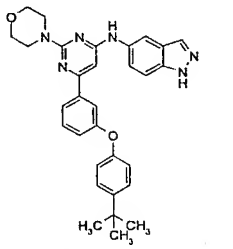
^1H NMR (DMSO+D_2O, 300MHz): 9.22 (1H, bs), 8.37 (2H, app d, *J*= 5.7*)*, 7.79 (1H, dd, *J*= 7.2, 5.4), 7.43, (2H, m). 7.30 (1H, app t, *J*= 7.5), 6.89 (1H, dd, *J*= 7.0, 2.1), 6.59 (1H, s), 3.6-3.8 (8H, m).

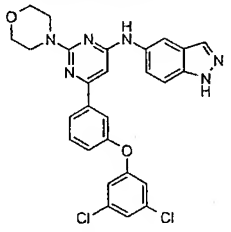
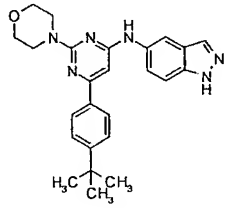
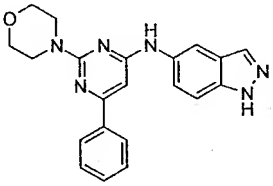
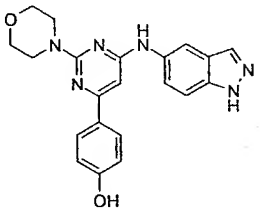
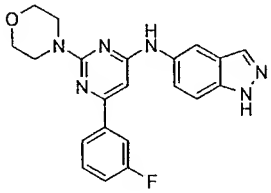
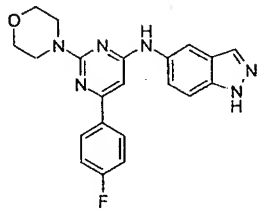
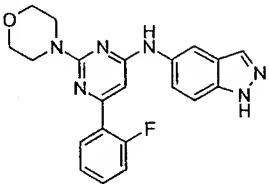
Compounds of the following Examples were synthesized following the synthetic method described above in Methods 1 and 2. The precursors are readily recognizable by one skilled in the art and are commercially available from Aldrich (Milwaukee, WI), Acros Organics (Pittsburgh, PA), Biosynth International (Naperville, IL), Asymchem International, Inc. (Durham, NC) Maybridge Chemical Company Ltd. (Cornwall), and/or UK Peakdale Molecular (High Peak, UK).

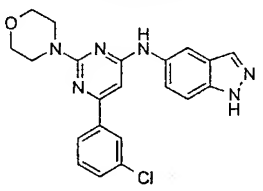
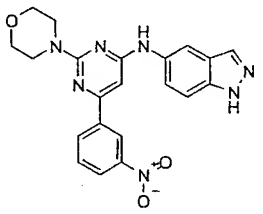
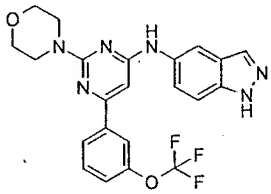
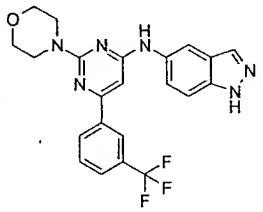
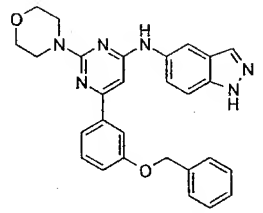
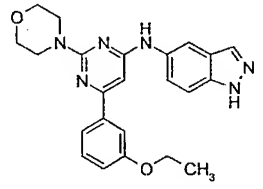
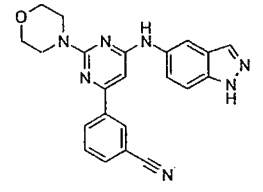
The compounds were named using ACD/Name v. 5.04, **2001** and Nomenclator (v. 6.0) from ChemInovation Software, Inc.

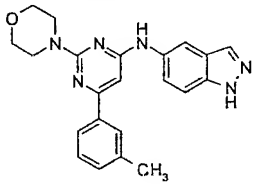
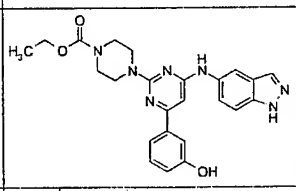
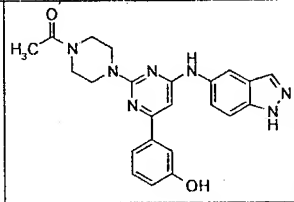
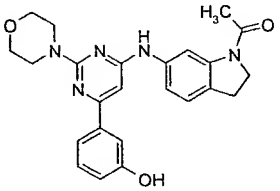
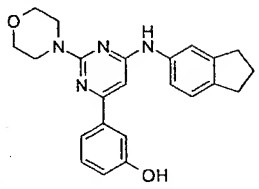
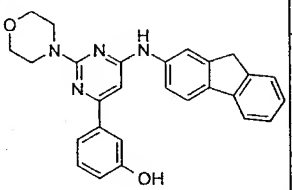
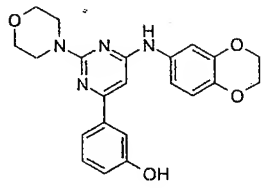
Example	Structure	Name	LC/MS m/z (MH+)
2		N-[6-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-morpholin-4-ylpyrimidin-4-yl]-1H-indazol-6-amine	431.5
3		4-(3-hydroxyphenyl)-6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidine-5-carboxylic acid	433.4
4		4-[3-(2-hydroxyethoxy)phenyl]-6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidine-5-carboxylic acid	477.5

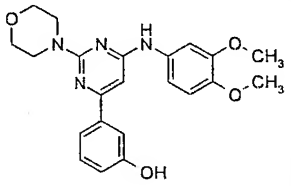
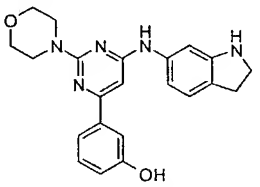
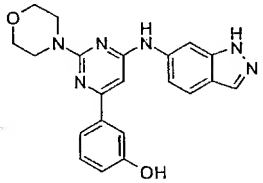
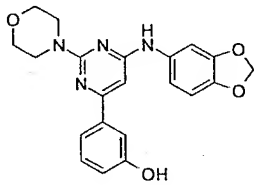
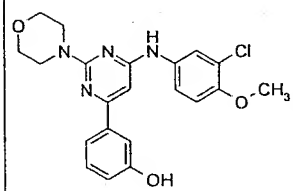
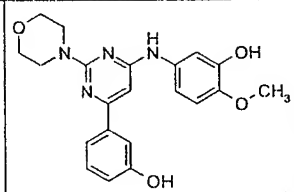
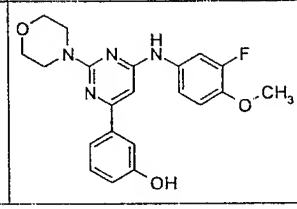
Example	Structure	Name	LC/MS m/z (MH+)
5		4-(1H-indazol-5-ylamino)-2-morpholin-4-yl-6-(4-phenoxyphenyl)pyrimidine-5-carboxylic acid	509.5
6		4-(2,3-dihydro-1,4-benzodioxin-6-yl)-6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidine-5-carboxylic acid	475.5
7		4-(1H-indazol-5-ylamino)-6-[4-(methylsulfonyl)phenyl]-2-morpholin-4-ylpyrimidine-5-carboxylic acid	495.5
8		4-[3-(4-tert-butylphenoxy)phenyl]-6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidine-5-carboxylic acid	565.6
9		4-[3-(3,5-dichlorophenoxy)phenyl]-6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidine-5-carboxylic acid	578.4
10		4-(4-tert-butylphenyl)-6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidine-5-carboxylic acid	473.5
11		4-(1H-indazol-5-ylamino)-2-morpholin-4-yl-6-phenylpyrimidine-5-carboxylic acid	417.4

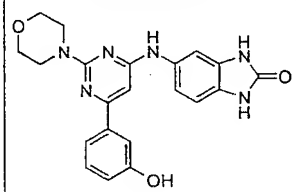
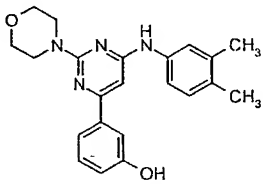
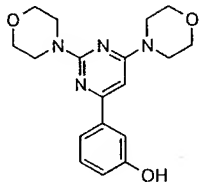
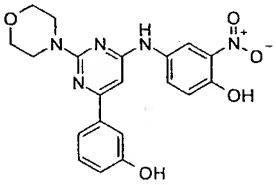
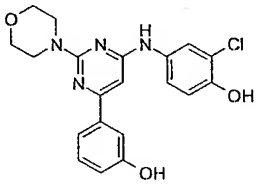
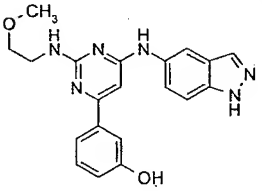
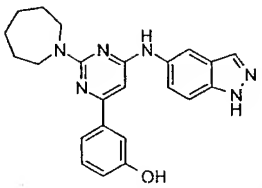
Example	Structure	Name	LC/MS m/z (MH+)
11a			
12		N-[6-(4-methoxy-3-methylphenyl)-2-morpholin-4-ylpyrimidin-4-yl]-1H-indazol-5-amine	417.5
13		2-{3-[6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenoxy}ethanol	433.5
14		N-[2-morpholin-4-yl-6-(4-phenoxyphenyl)pyrimidin-4-yl]-1H-indazol-5-amine	465.5
15		N-{6-[4-(methylsulfonyl)phenyl]-2-morpholin-4-ylpyrimidin-4-yl}-1H-indazol-5-amine	451.5
16		N-{6-[3-(4-tert-butylphenoxy)phenyl]-2-morpholin-4-ylpyrimidin-4-yl}-1H-indazol-5-amine	521.6

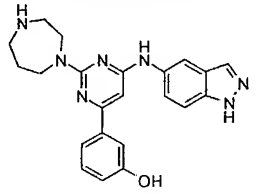
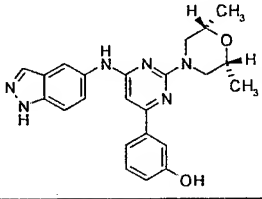
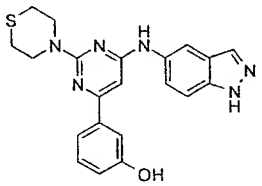
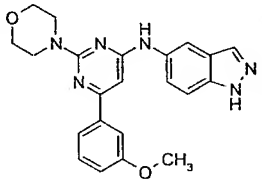
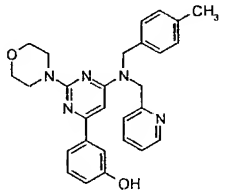
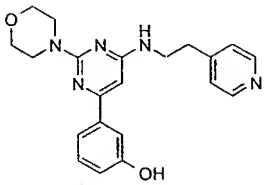
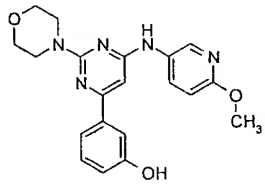
Example	Structure	Name	LC/MS m/z (MH+)
17		N-{6-[3-(3,5-dichlorophenoxy)phenyl]-2-morpholin-4-ylpyrimidin-4-yl}-1H-indazol-5-amine	534.4
18		N-[6-(4-tert-butylphenyl)-2-morpholin-4-ylpyrimidin-4-yl]-1H-indazol-5-amine	429.5
19		N-(2-morpholin-4-yl-6-phenylpyrimidin-4-yl)-1H-indazol-5-amine	373.4
20		4-[6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	389.4
21		N-[6-(3-fluorophenyl)-2-morpholin-4-ylpyrimidin-4-yl]-1H-indazol-5-amine	391.4
22		N-[6-(4-fluorophenyl)-2-morpholin-4-ylpyrimidin-4-yl]-1H-indazol-5-amine	391.4
23		N-[6-(2-fluorophenyl)-2-morpholin-4-ylpyrimidin-4-yl]-1H-indazol-5-amine	391.4

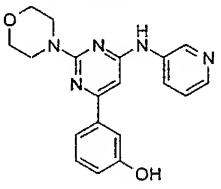
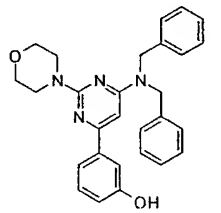
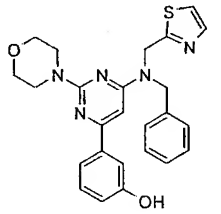
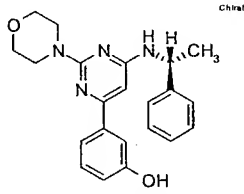
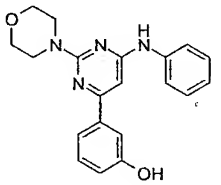
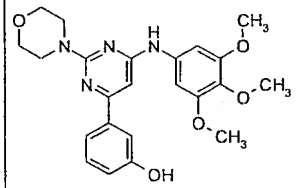
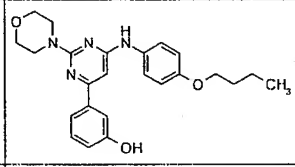
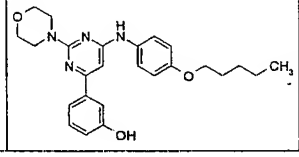
Example	Structure	Name	LC/MS m/z (MH+)
24		N-[6-(3-chlorophenyl)-2-morpholin-4-ylpyrimidin-4-yl]-1H-indazol-5-amine	407.9
25		N-[2-morpholin-4-yl-6-(3-nitrophenyl)pyrimidin-4-yl]-1H-indazol-5-amine	418.4
26		N-{2-morpholin-4-yl-6-[3-(trifluoromethoxy)phenyl]pyrimidin-4-yl}-1H-indazol-5-amine	457.4
27		N-{2-morpholin-4-yl-6-[3-(trifluoromethyl)phenyl]pyrimidin-4-yl}-1H-indazol-5-amine	441.4
28		N-{6-[3-(benzyloxy)phenyl]-2-morpholin-4-ylpyrimidin-4-yl}-1H-indazol-5-amine	479.6
29		N-[6-(3-ethoxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]-1H-indazol-5-amine	417.5
30		3-[6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]benzonitrile	398.4

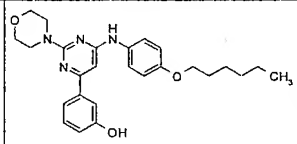
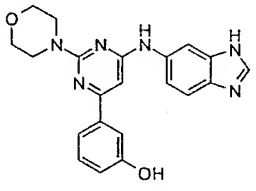
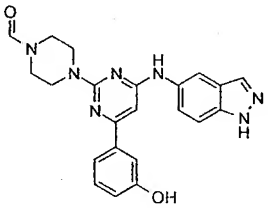
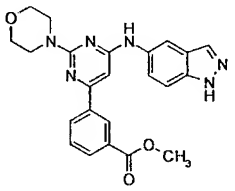
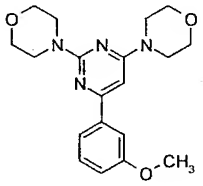
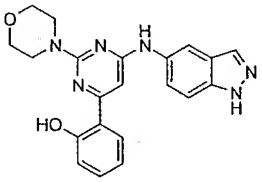
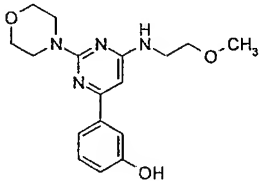
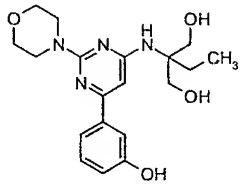
Example	Structure	Name	LC/MS m/z (MH+)
31		N-[6-(3-methylphenyl)-2-morpholin-4-ylpyrimidin-4-yl]-1H-indazol-5-amine	387.5
32		ethyl 4-[4-(3-hydroxyphenyl)-6-(1H-indazol-5-ylamino)pyrimidin-2-yl]piperazine-1-carboxylate	460.5
33		3-[2-(4-acetylpiperazin-1-yl)-6-(1H-indazol-5-ylamino)pyrimidin-4-yl]phenol	430.5
34		3-{6-[(1-acetyl-2,3-dihydro-1H-indol-6-yl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	432.5
35		3-[6-(2,3-dihydro-1H-inden-5-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	389.5
36		3-[6-(9H-fluoren-2-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	437.5
37		3-[6-(2,3-dihydro-1,4-benzodioxin-6-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	407.4

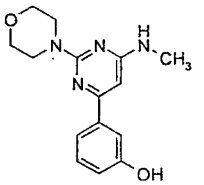
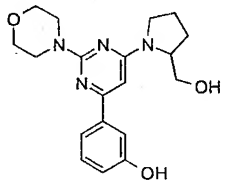
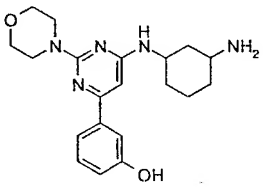
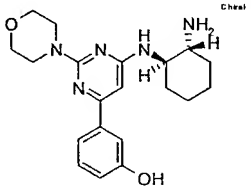
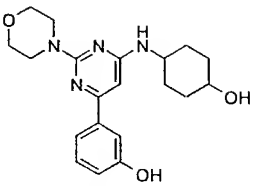
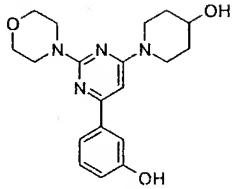
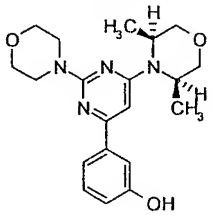
Example	Structure	Name	LC/MS m/z (MH+)
38		3-{6-[(3,4-dimethoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	409.5
39		3-[6-(2,3-dihydro-1H-indol-6-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	390.5
40		3-[6-(1H-indazol-6-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	389.4
41		3-[6-(1,3-benzodioxol-5-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	393.4
42		3-{6-[(3-chloro-4-methoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	413.9
43		5-{[6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]amino}-2-methoxyphenol	395.4
44		3-{6-[(3-fluoro-4-methoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	397.4

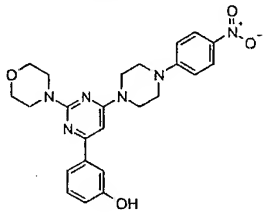
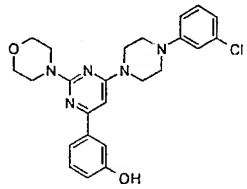
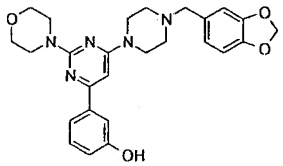
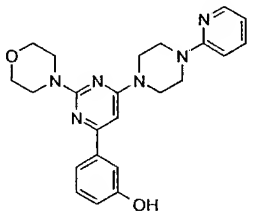
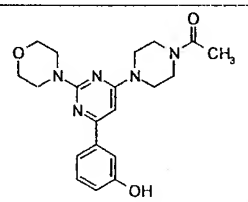
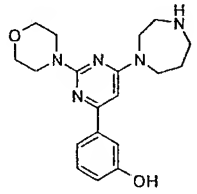
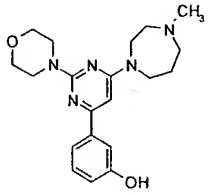
Example	Structure	Name	LC/MS m/z (MH+)
45		5-{[6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]amino}-1,3-dihydro-2H-benzimidazol-2-one	405.4
46		3-{6-[(3,4-dimethylphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	377.5
47		3-(2,6-dimorpholin-4-ylpyrimidin-4-yl)phenol	343.4
48		4-{[6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]amino}-2-nitrophenol	410.4
49		2-chloro-4-{[6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]amino}phenol	399.8
50		3-{6-(1H-indazol-5-ylamino)-2-[(2-methoxyethyl)amino]pyrimidin-4-yl}phenol	377.4
51		3-[2-azepan-1-yl-6-(1H-indazol-5-ylamino)pyrimidin-4-yl]phenol	401.5

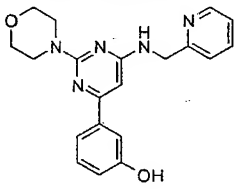
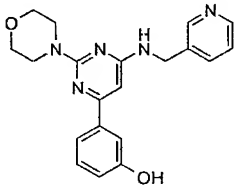
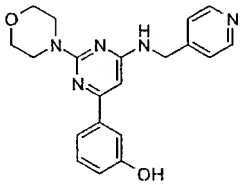
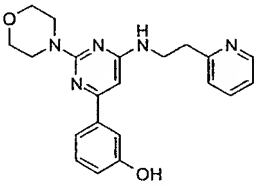
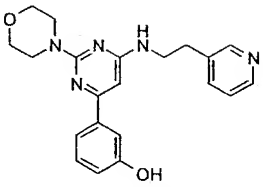
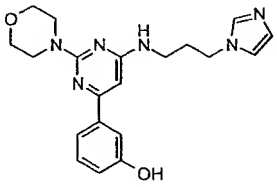
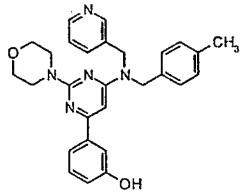
Example	Structure	Name	LC/MS m/z (MH+)
52		3-[2-(1,4-diazepan-1-yl)-6-(1H-indazol-5-ylamino)pyrimidin-4-yl]phenol	402.5
53		3-[2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-6-(1H-indazol-5-ylamino)pyrimidin-4-yl]phenol	417.5
54		3-[6-(1H-indazol-5-ylamino)-2-thiomorpholin-4-ylpyrimidin-4-yl]phenol	405.5
55		N-[6-(3-methoxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]-1H-indazol-5-amine	403.5
56		3-{6-[(4-methylbenzyl)(pyridin-2-ylmethyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	468.6
57		3-{2-morpholin-4-yl-6-[(2-pyridin-4-ylethyl)amino]pyrimidin-4-yl}phenol	378.4
58		3-{6-[(6-methoxypyridin-3-yl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	380.4

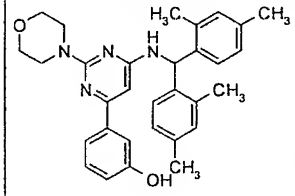
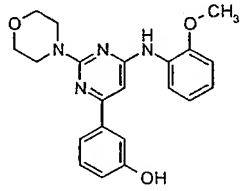
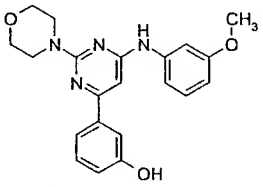
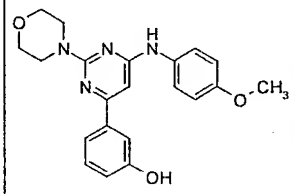
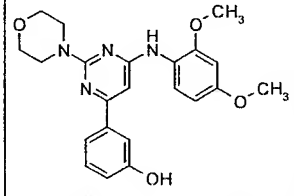
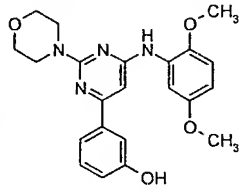
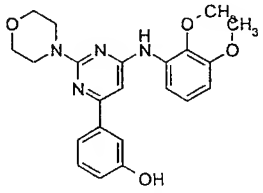
Example	Structure	Name	LC/MS m/z (MH+)
59		3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenol	350.4
60		3-[6-(dibenzylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	453.6
61		3-{6-[benzyl(1,3-thiazol-2-ylmethyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	460.6
62		3-(2-morpholin-4-yl-6-{[(1R)-1-phenylethyl]amino}pyrimidin-4-yl)phenol	377.5
63		3-(6-anilino-2-morpholin-4-ylpyrimidin-4-yl)phenol	349.4
64		3-{2-morpholin-4-yl-6-[(3,4,5-trimethoxyphenyl)amino]pyrimidin-4-yl}phenol	439.5
65		3-{6-[(4-butoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	421.5
66		3-(2-morpholin-4-yl-6-{[4-(pentyloxy)phenyl]amino}pyrimidin-4-yl)phenol	435.5

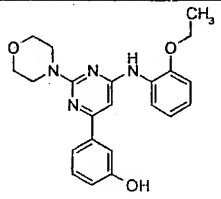
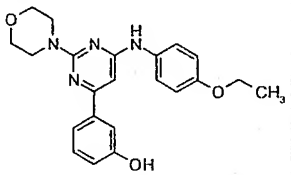
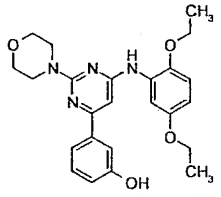
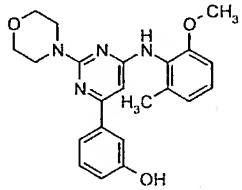
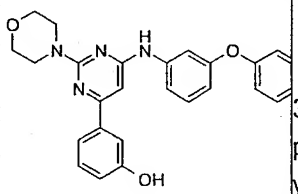
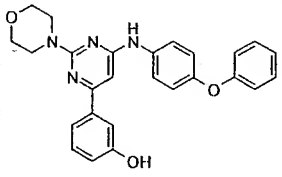
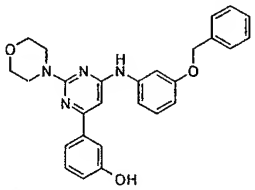
Example	Structure	Name	LC/MS m/z (MH+)
67		3-(6-{[4-(hexyloxy)phenyl]amino}-2-morpholin-4-ylpyrimidin-4-yl)phenol	449.6
68		3-[6-(1H-benzimidazol-6-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	389.4
69		4-[4-(3-hydroxyphenyl)-6-(1H-indazol-5-ylamino)pyrimidin-2-yl]piperazine-1-carbaldehyde	416.5
70		methyl 3-[6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]benzoate	431.5
71		4-[4-(3-methoxyphenyl)-6-morpholin-4-ylpyrimidin-2-yl]morpholine	357.4
72		2-[6-(1H-indazol-5-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	389.4
73		3-{6-[(2-methoxyethyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	331.4
74		2-ethyl-2-{[6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]amino}propane-1,3-diol	375.4

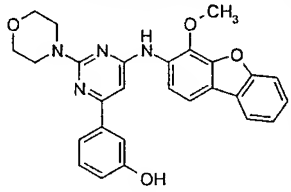
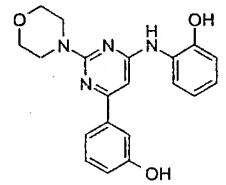
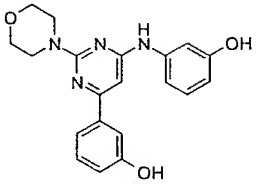
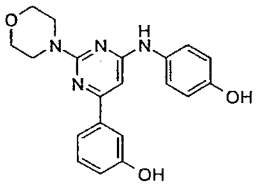
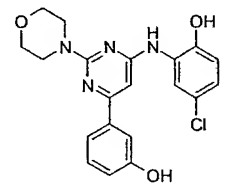
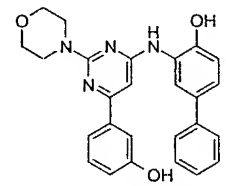
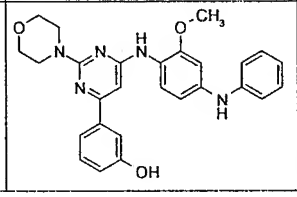
Example	Structure	Name	LC/MS m/z (MH+)
75		3-[6-(methylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	287.3
76		3-{6-[2-(hydroxymethyl)pyrrolidin-1-yl]-2-morpholin-4-ylpyrimidin-4-yl}phenol	357.4
77		3-{6-[(3-aminocyclohexyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	370.5
78		3-(6-{[(1R,2R)-2-aminocyclohexyl]amino}-2-morpholin-4-ylpyrimidin-4-yl)phenol	370.5
79		3-{6-[(4-hydroxycyclohexyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	371.4
80		1-[6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]piperidin-4-ol	357.4
81		3-{6-[(3R,5S)-3,5-dimethylmorpholin-4-yl]-2-morpholin-4-ylpyrimidin-4-yl}phenol	371.4

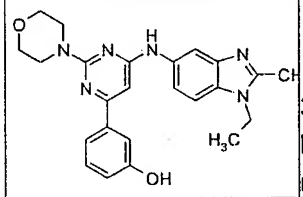
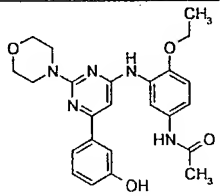
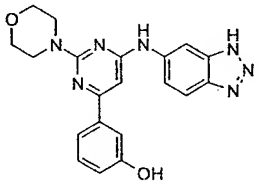
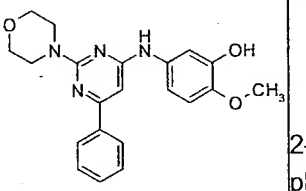
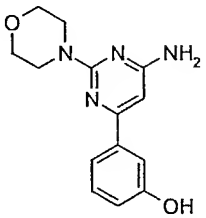
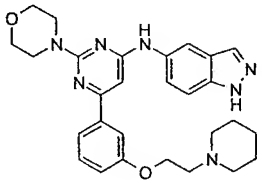
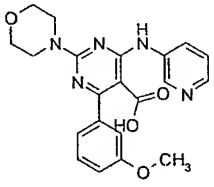
Example	Structure	Name	LC/MS m/z (MH+)
82		3-{2-morpholin-4-yl-6-[4-(4-nitrophenyl)piperazin-1-yl]pyrimidin-4-yl}phenol	463.5
83		3-{6-[4-(3-chlorophenyl)piperazin-1-yl]-2-morpholin-4-ylpyrimidin-4-yl}phenol	453.0
84		3-{6-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-2-morpholin-4-ylpyrimidin-4-yl}phenol	476.5
85		3-[2-morpholin-4-yl-6-(4-pyridin-2-ylpiperazin-1-yl)pyrimidin-4-yl]phenol	419.5
86		3-[6-(4-acetylpiperazin-1-yl)-2-morpholin-4-ylpyrimidin-4-yl]phenol	384.4
87		3-[6-(1,4-diazepan-1-yl)-2-morpholin-4-ylpyrimidin-4-yl]phenol	356.4
88		3-[6-(4-methyl-1,4-diazepan-1-yl)-2-morpholin-4-ylpyrimidin-4-yl]phenol	370.5

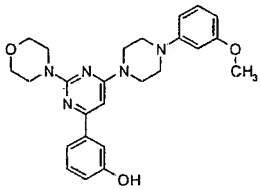
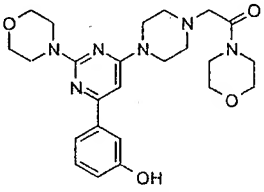
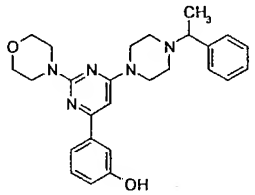
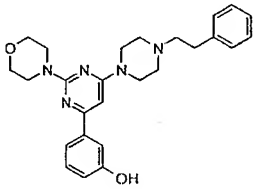
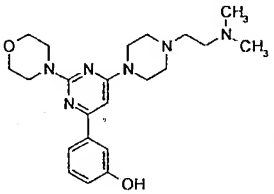
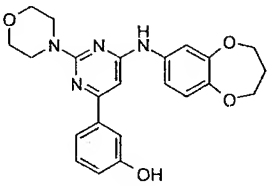
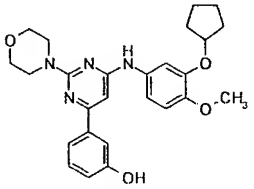
Example	Structure	Name	LC/MS m/z (MH+)
89		3-{2-morpholin-4-yl-6-[(pyridin-2-ylmethyl)amino]pyrimidin-4-yl}phenol	364.4
90		3-{2-morpholin-4-yl-6-[(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}phenol	364.4
91		3-{2-morpholin-4-yl-6-[(pyridin-4-ylmethyl)amino]pyrimidin-4-yl}phenol	364.4
92		3-{2-morpholin-4-yl-6-[(2-pyridin-2-ylethyl)amino]pyrimidin-4-yl}phenol	378.4
93		3-{2-morpholin-4-yl-6-[(2-pyridin-3-ylethyl)amino]pyrimidin-4-yl}phenol	378.4
94		3-(6-{[3-(1H-imidazol-1-yl)propyl]amino}-2-morpholin-4-ylpyrimidin-4-yl)phenol	381.4
95		3-{6-[(4-methylbenzyl)(pyridin-3-ylmethyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	468.6

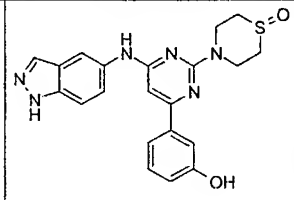
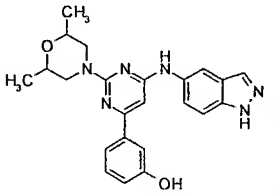
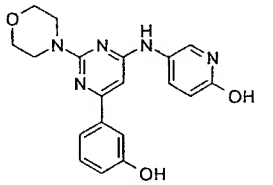
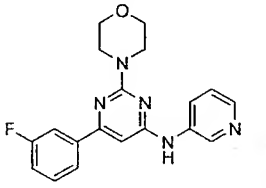
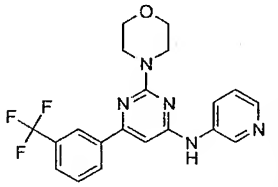
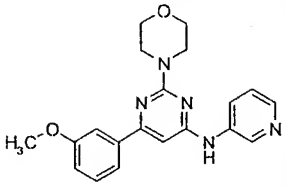
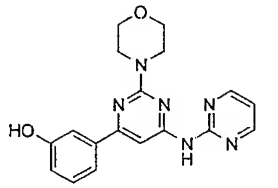
Example	Structure	Name	LC/MS m/z (MH+)
96		3-(6-{[bis(2,4-dimethylphenyl)methyl]amino}-2-morpholin-4-ylpyrimidin-4-yl)phenol	495.6
97		3-{6-[(2-methoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	379.4
98		3-{6-[(3-methoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	379.4
99		3-{6-[(4-methoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	379.4
100		3-{6-[(2,4-dimethoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	409.5
101		3-{6-[(2,5-dimethoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	409.5
102		3-{6-[(2,3-dimethoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	409.5

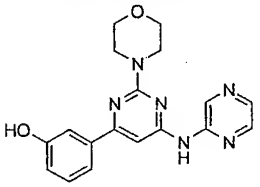
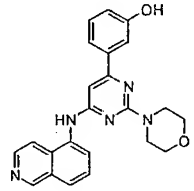
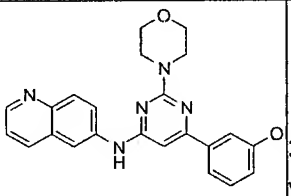
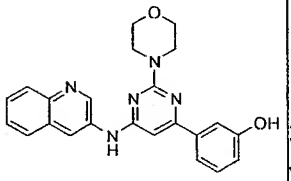
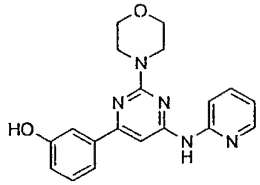
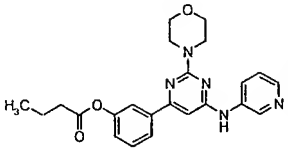
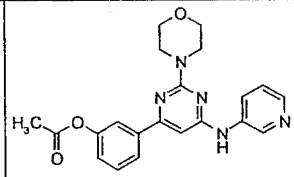
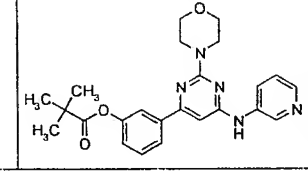
Example	Structure	Name	LC/MS m/z (MH+)
103		3-{6-[(2-ethoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	393.5
104		3-{6-[(4-ethoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	393.5
105		3-{6-[(2,5-diethoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	437.5
106		3-{6-[(2-methoxy-6-methylphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	393.5
107		3-{2-morpholin-4-yl-6-[(3-phenoxyphenyl)amino]pyrimidin-4-yl}phenol	441.5
108		3-{2-morpholin-4-yl-6-[(4-phenoxyphenyl)amino]pyrimidin-4-yl}phenol	441.5
109		3-(6-{[3-(benzyloxy)phenyl]amino}-2-morpholin-4-ylpyrimidin-4-yl)phenol	455.5

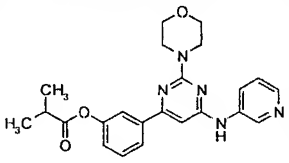
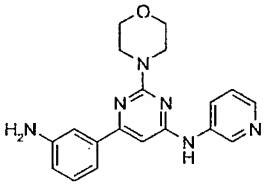
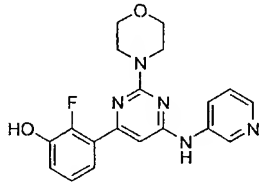
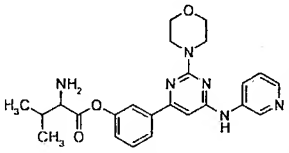
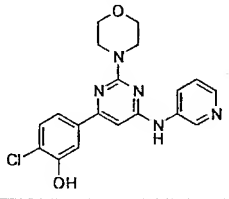
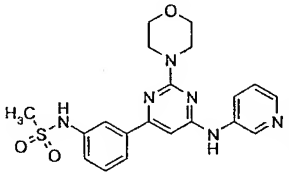
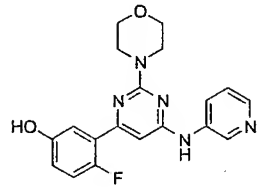
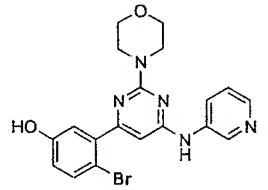
Example	Structure	Name	LC/MS m/z (MH+)
110		3-{6-[(4-methoxydibenzo[b,d]furan-3-yl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	469.5
111		2-{[6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]amino}phenol	365.4
112		3-{6-[(3-hydroxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	365.4
113		3-{6-[(4-hydroxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	365.4
114		4-chloro-2-{[6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]amino}phenol	399.8
115		3-{[6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]amino}-1,1'-biphenyl-4-ol	441.5
116		3-{6-[(4-anilino-2-methoxyphenyl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	470.5

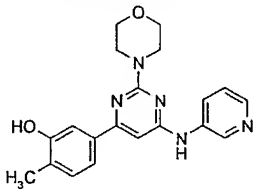
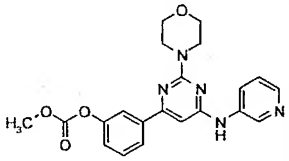
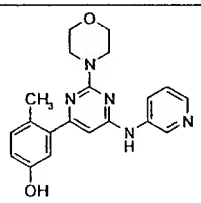
Example	Structure	Name	LC/MS m/z (MH+)
117		3-{6-[(1-ethyl-2-methyl-1H-benzimidazol-5-yl)amino]-2-morpholin-4-ylpyrimidin-4-yl}phenol	431.5
118		N-(4-ethoxy-3-{[6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]amino}phenyl)acetamide	450.5
119		3-[6-(1H-1,2,3-benzotriazol-6-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	390.4
120		2-methoxy-5-[(2-morpholin-4-yl-6-phenylpyrimidin-4-yl)amino]phenol	379.4
121		3-(6-amino-2-morpholin-4-ylpyrimidin-4-yl)phenol	273.3
122		N-{2-morpholin-4-yl-6-[3-(2-piperidin-1-ylethoxy)phenyl]pyrimidin-4-yl}-1H-indazol-5-amine	500.6
123		4-(3-methoxyphenyl)-2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidine-5-carboxylic acid	408.4

Example	Structure	Name	LC/MS m/z (MH+)
124		3-{6-[4-(3-methoxyphenyl)piperazin-1-yl]-2-morpholin-4-ylpyrimidin-4-yl}phenol	448.5
125		3-{2-morpholin-4-yl-6-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]pyrimidin-4-yl}phenol	469.6
126		3-{2-morpholin-4-yl-6-[4-(1-phenylethyl)piperazin-1-yl]pyrimidin-4-yl}phenol	446.6
127		3-{2-morpholin-4-yl-6-[4-(2-phenylethyl)piperazin-1-yl]pyrimidin-4-yl}phenol	446.6
128		3-(6-{4-[2-(dimethylamino)ethyl]piperazin-1-yl}-2-morpholin-4-ylpyrimidin-4-yl)phenol	413.5
129		3-[6-(3,4-dihydro-2H-1,5-benzodioxepin-7-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	421.5
130		3-(6-{[3-(cyclopentyloxy)-4-methoxyphenyl]amino}-2-morpholin-4-ylpyrimidin-4-yl)phenol	463.5

Example	Structure	Name	LC/MS m/z (MH+)
131		3-[6-(1H-indazol-5-ylamino)-2-(1-oxidothiomorpholin-4-yl)pyrimidin-4-yl]phenol	421.5
132		3-[2-(2,6-dimethylmorpholin-4-yl)-6-(1H-indazol-5-ylamino)pyrimidin-4-yl]phenol	417.5
133		5-{[6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-yl]amino}pyridin-2-ol	366.4
134		6-(3-fluorophenyl)-2-morpholin-4-yl-N-pyridin-3-ylpyrimidin-4-amine	352.4
135		2-morpholin-4-yl-N-pyridin-3-yl-6-[3-(trifluoromethyl)phenyl]pyrimidin-4-amine	402.4
136		6-(3-methoxyphenyl)-2-morpholin-4-yl-N-pyridin-3-ylpyrimidin-4-amine	364.4
137		3-[2-morpholin-4-yl-6-(pyrimidin-2-ylamino)pyrimidin-4-yl]phenol	351.4

Example	Structure	Name	LC/MS m/z (MH+)
138		3-[2-morpholin-4-yl-6-(pyrazin-2-ylamino)pyrimidin-4-yl]phenol	351.4
139		3-[6-(isoquinolin-5-ylamino)-2-morpholin-4-ylpyrimidin-4-yl]phenol	400.5
140		3-[2-morpholin-4-yl-6-(quinolin-6-ylamino)pyrimidin-4-yl]phenol	400.5
141		3-[2-morpholin-4-yl-6-(quinolin-3-ylamino)pyrimidin-4-yl]phenol	400.5
142		3-[2-morpholin-4-yl-6-(pyridin-2-ylamino)pyrimidin-4-yl]phenol	350.4
143		3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenyl butyrate	420.5
144		3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenyl acetate	392.4
145		3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenyl pivalate	434.5

Example	Structure	Name	LC/MS m/z (MH+)
146		3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenyl 2-methylpropanoate	420.5
147		6-(3-aminophenyl)-2-morpholin-4-yl-N-pyridin-3-ylpyrimidin-4-amine	349.4
148		2-fluoro-3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenol	368.4
149		3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenyl valinate	449.5
150		2-chloro-5-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenol	384.8
151		N-{3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenyl}methanesulfonamide	427.5
152		4-fluoro-3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenol	368.4
153		4-bromo-3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenol	429.3

Example	Structure	Name	LC/MS m/z (MH+)
154		2-methyl-5-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenol	364.4
155		methyl 3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenyl carbonate	408.4
156		4-methyl-3-[2-morpholin-4-yl-6-(pyridin-3-ylamino)pyrimidin-4-yl]phenol	364.4
157		6-(3-hydroxyphenyl)-2-morpholin-4-ylpyrimidin-4-ol	274.3

Example 158

PI3K Assay Procedures

Method 1: Homogenous solution phase assay

Compounds to be tested are dissolved in DMSO and directly distributed to 384-well flashplates at 1.25 µL per well. To start the reaction, 20 µL of 6 nM PI3 kinase are added into each well followed by 20 µL of 400 nM ATP containing a trace of radio-labeled ATP and 900 nM 1-alpha-phosphatidylinositol (PI). The plates are briefly centrifuged to remove any air gap. The reaction is performed for 15 minutes and then stopped by the addition of 20 µL of 100 mM EDTA. The stopped reaction is incubated overnight at RT to allow the lipid substrate to bind by hydrophobic interaction to the surface of the flashplate. The liquid in the wells is then washed away, and the labeled substrate is detected with scintillation counting.

Method 2: One step solid phase assay

This method is similar to Method 1 except that the lipid substrate (1-alpha-phosphatidylinositol) is first dissolved in a coating buffer and incubated on flashplate at room temperature over night to allow the lipid substrate to bind by hydrophobic interaction to the surface of the flashplate. Unbound substrate is then washed away. On the day of assay, 20 μL of 6 nM PI3 kinase are added into each well followed by 20 μL of 400 nM ATP containing trace of radio-labeled ATP. Compounds are added together with enzyme and ATP to the lipid-coated plates. The plates are briefly centrifuged to remove any air gap. The reaction is performed for two to three hours. The reaction is stopped by addition of 20 μL of 100 mM EDTA or by immediate plate washing. Phosphorylated lipid substrate is detected with scintillation counting.

The compounds of Examples 11a, 13, 19, 34-49, 51-53, 55, 57-59, 61-64, 68, 71-76, 79, 81, 82, 85-87, 89-91, 118, 119, 121, 122, 124 and 133-156 displayed an IC_{50} value of less than 20 μM with respect to PI3K when tested in the homogeneous solution assay (Method 1), as described above. The compounds of Examples 20, 21, 23, 47, 55-60, 62, 63, 65, 70, 71-75, 77-95, 97-120, 122-125, 127, 129, 130, 133, 137 and 143-155 displayed an IC_{50} value of less than 20 μM with respect to PI3K when tested in the one step solid phase assay (Method 2), as described above.

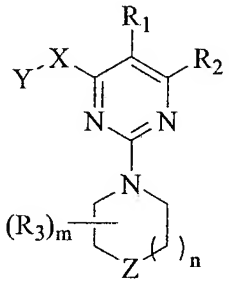
It should be understood that the organic compounds according to the invention may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the invention encompasses any tautomeric form of the drawn structure.

It is understood that the invention is not limited to the embodiments set forth herein for illustration, but embraces all such forms thereof as come within the scope of the above disclosure.

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

ABSTRACT OF THE DISCLOSURE

Organic compounds having formula I are provided where the variables have the values described herein.



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Pharmaceutical formulations include the organic compounds or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier and combinations with other agents. A method of treating a patient comprises administering a pharmaceutical formulation according to the invention to a patient in need thereof.

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